(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 October 2006 (26.10.2006)

PCT

(10) International Publication Number
WO 2006/113695 A1

(51) International Patent Classification:
A61K 31/337 (2006.01) *A61K 31/16* (2006.01)
A61K 31/165 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2006/014531

(22) International Filing Date: 13 April 2006 (13.04.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/672,139 15 April 2005 (15.04.2005) US

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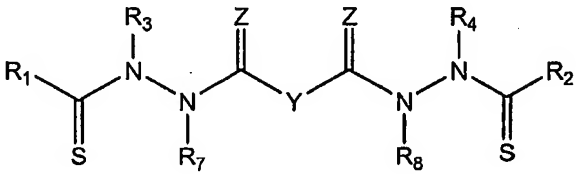
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATION CANCER THERAPY WITH BIS(THIOHYDRAZIDE) AMIDE COMPOUNDS



(I)

(57) Abstract: A method of treating a subject with cancer includes the step of co-administering to the subject over three to five weeks, a taxane in an amount of between about 243 μmol/m2 to 315 μmol/m2 (e.g., equivalent to paclitaxel in about 210-270 mg/m2); and a bis(thiohydrazide amide) in an amount between about 1473 μmol/m2 and about 1722 μmol/m2 (e.g., Compound (1) in about 590 - 690 mg/m2). The bis(thiohydrazide amide) is represented by Structural Formula (I), Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group. R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring. R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an otionally substituted aryl group. Z is O or S.

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AM2

COMBINATION CANCER THERAPY WITH BIS(THIOHYDRAZIDE) AMIDE COMPOUNDS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/672,139, filed on April 15, 2005. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

The taxanes are an important class of anticancer agents. In particular, Taxol™ (paclitaxel) is an effective anticancer agent, especially in the treatment of ovarian cancer, metastatic breast cancer, non-small cell lung cancer (NSCLC) and AIDS-related Kaposi's sarcoma. However, there is still a significant need in the art for improvement in the efficacy of paclitaxel therapy, both in terms of the proportion of patients who respond to therapy and the survival benefit imparted. Moreover, administration of Taxol has side effects, including reducing immune function by reducing natural killer (NK) cell activity.

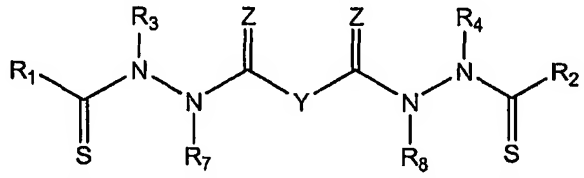
In an attempt to improve efficacy, paclitaxel is sometimes used in combination with other anticancer agents. For example, carboplatin in the treatment of NSCLC. Such combinations can have an additive benefit or increased response rate, but can tend to also combine the side effect profiles of each agent. Other agents have been researched, for example, bis(thiohydrazide amides) have been tested in animal models as described in U.S. Patent Nos. 6,800,660, 6,762,204, U.S. Pat. Appl. Ser. Nos. 10/345,885 filed January 15, 2003, and 10/758,589, January 15, 2004, the entire teachings of which are incorporated herein by reference.

However, there is still an urgent need for particular combination therapies that can enhance the antitumor effects of paclitaxel without further increasing side effects suffered by patients.

SUMMARY OF THE INVENTION

It is now found that certain bis(thiohydrazide) amide and taxane combinations are surprisingly effective at treating subjects with cancer without further increasing side effects. The particular combination therapies disclosed herein demonstrate surprising biological activity by raising Hsp70 levels (see Example 3), by demonstrating significant anticancer effects (see Examples 4-5), and by halting or reversing side effects (see Examples 4-5) such as the reduction in natural killer (NK) cell activity typically associated with Taxol™ administration.

A method of treating a subject with cancer includes the step of co-administering to the subject over three to five weeks, a taxane in an amount of between about 243 μmol/m2 to 315 μmol/m2 (e.g., equivalent to paclitaxel in about 210-270 mg/m2); and a bis(thiohydrazide amide) in an amount between about 1473 μmol/m2 and about 1722 μmol/m2 (e.g., Compound (1) in about 590 - 690 mg/m2). The bis(thiohydrazide amide) is represented by Structural Formula I:



II

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group.

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring.

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group.

Z is O or S.

In various embodiments, a method of treating a subject with cancer includes administering to the subject effective amounts of each of a platinum anticancer

compound; a taxane or a pharmaceutically acceptable salt or solvate thereof; and a bis(thiohydrazide amide) represented by Structural Formula I or a pharmaceutically acceptable salt or solvate thereof.

In various embodiments, a method of treating a subject with cancer includes administering to the subject once every three weeks, independently or together a taxane in an amount of about 205 μmol/m2 (e.g., paclitaxel in about 175 mg/m2); and a bis(thiohydrazide amide) represented by Structural Formula I or a pharmaceutically acceptable salt or solvate thereof in an amount between about 220 μmol/m2 and about 1310 μmol/m2 (e.g., Compound (1) in about 88 - 525 mg/m2).

In various embodiments, a pharmaceutical composition includes a pharmaceutically acceptable carrier or diluent. In some embodiments, the molar ratio of bis(thiohydrazide amide) to taxane can be between about 5.5:1 and about 5.9:1, in certain embodiments, between about 2.7:1 and about 2.9:1, and in particular embodiments, between about 4.1:1 and about 4.5:1.

In various embodiments, the invention includes the use of a bis(thiohydrazide amide) for the manufacture of medicament for treating cancer in combination with a taxane in each of the molar ratios described above. In some embodiments, the invention includes the use of a bis(thiohydrazide amide) and taxane for the manufacture of medicament for treating cancer in each of the molar ratios described above.

The taxanes employed in the invention, *e.g.*, paclitaxel, are described in the Detailed Description section below.

In various embodiments, a pharmaceutically acceptable salt or solvate of either the bis(thiohydrazide)amide or taxane anticancer agents can be employed, optionally with a pharmaceutically acceptable carrier or diluent. In certain embodiments, a pharmaceutical composition includes the bis(thiohydrazide) amide, the taxane, and a pharmaceutically acceptable carrier or diluent.

The methods are particularly effective for treating the claimed cancers as demonstrated in the Examples, and halting or reversing side effects such as the reduction in natural killer (NK) cell activity typically associated with Taxol™ administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs 1A, 1B, and 1C are bar graphs showing the percent increase in Hsp70 plasma levels associated with administration of the Compound (1)/paclitaxel combination therapy at 1 hour (FIG 1A), 5 hours (FIG 1B), and 8 hours (FIG 1C) after administration.

DETAILED DESCRIPTION OF THE INVENTION

A description of preferred embodiments of the invention follows.

In various embodiments, a method of treating a subject with cancer includes the step of co-administering to the subject over three to five weeks, a taxane in an amount of between about 243 μmol/m2 to 315 μmol/m2 (e.g., equivalent to paclitaxel in about 210-270 mg/m2); and a bis(thiohydrazide amide) (e.g., as represented by Structural Formula I) in an amount between about 1473 μmol/m2 and about 1722 μmol/m2 (e.g., Compound (1) in about 590 - 690 mg/m2).

A subject, e.g., typically a human subject, can be treated for any cancer described herein. Typically, the cancer can be a soft tissue sarcoma (e.g., typically soft tissue sarcomas other than GIST) or metastatic melanoma. In some embodiments, the cancer is metastatic melanoma.

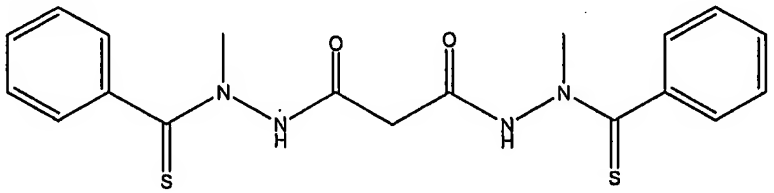
In some embodiments, the the taxane and the bis(thio-hydrazide) amide can each be administered in three equal weekly doses for three weeks of a four week period. In preferred embodiments, the four week administration period can be repeated until the cancer is in remission.

The taxane can be any taxane defined herein. In particular embodiments, the taxane is paclitaxel intravenously administered in a weekly dose of about 94 μmol/m2 (80 mg/m2).

In various embodiments, the bis(thiohydrazide amide) can be intravenously administered in a weekly dose of between about 500 μmol/m2 and about 562 μmol/m2, or more typically in a weekly dose of about 532 μmol/m2. (e.g., Compound (1) in about 590 - 690 mg/m2).

In some embodiments, the subject is treated for metastatic melanoma. In certain embodiments, the subject is treated for soft tissue sarcomas other than GIST.

In preferred embodiments, a method of treating a human subject with cancer includes intravenously administering to the subject in a four week period, three equal weekly doses of paclitaxel in an amount of about 94 μmol/m2; and a bis(thiohydrazide amide) represented by the following Structural Formula:



or a pharmaceutically acceptable salt or solvate thereof in an amount of about 532 μmol/m2. Typically, the cancer is a soft tissue sarcomas (e.g., typically soft tissue sarcomas other than GIST) or metastatic melanoma.

In various embodiments, the subject can be intravenously administered between about 220 μmol/m2 and about 1310 μmol/m2 (e.g., Compound (1) in about 88 - 525 mg/m2) of the bis(thiohydrazide amide) once every 3 weeks, generally between about 220 μmol/m2 and about 1093 μmol/m2 (e.g., Compound (1) in about 88 - 438 mg/m2) once every 3 weeks, typically between about 624 μmol/m2 and about 1124 μmol/m2 m2 (e.g., Compound (1) in about 250-450 mg/m2), more typically between about 811 μmol/m2 and about 936 μmol/m2 m2 (e.g., Compound (1) in about 325-375 mg/m2), or in particular embodiments, about 874 μmol/m2 ((e.g., Compound (1) in about 350 mg/m2). In particular embodiments, the subject can be intravenously administered between about 582 μmol/m2 and about 664 μmol/m2 (e.g., Compound (1) in about 233 - 266 mg/m2) of the bis(thiohydrazide amide) once every 3 weeks. In certain embodiments, the bis(thiohydrazide amide) is in an amount of about 664 μmol/m2 (e.g., Compound (1) in about 266 mg/m2).

In various embodiments, the subject can be intravenously administered between about 200 μmol/m2 to about 263 μmol/m2 of the taxane as paclitaxel once every 3 weeks (e.g., paclitaxel in about 175-225 mg/m2). In some embodiments, the subject can be intravenously administered between about 200 μmol/m2 to about 234 μmol/m2 of the taxane as paclitaxel once every 3 weeks (e.g., paclitaxel in about 175-200

mg/m2). In certain embodiments, the paclitaxel is administered in an amount of about 234 μmol/m2 (200 mg/m2). In certain embodiments, the paclitaxel is administered in an amount of about 205 μmol/m2 (175 mg/m2)

In various embodiments, the taxane, e.g., paclitaxel, and the bis(thiohydrazide amide), e.g., Compound (1), can be administered together in a single pharmaceutical composition.

In various embodiments, a method of treating a subject with cancer includes administering to the subject once every three weeks, independently or together a taxane in an amount of about 205 μmol/m2 (e.g., paclitaxel in about 175 mg/m2); and a bis(thiohydrazide amide) represented by Structural Formula I or a pharmaceutically acceptable salt or solvate thereof in an amount between about 220 μmol/m2 and about 1310 μmol/m2 (e.g., Compound (1) in about 88 - 525 mg/m2).Typically, the taxane is paclitaxel intravenously administered in an amount of about 205 μmol/m2. The bis(thiohydrazide amide) can typically be intravenously administered between about 220 μmol/m2 and about 1093 μmol/m2 (e.g., Compound (1) in about 88 - 438 mg/m2), more typically between about 749 μmol/m2 and about 999 μmol/m2 (e.g., compound (1) in about 300-400 mg/m2), in some embodiments between about 811 μmol/m2 and about 936 μmol/m2 (e.g., Compound (1) in about 325-375 mg/m2). In certain embodiments, the bis(thiohydrazide amide) can be Compound (1) intravenously administered between about 874 μmol/m2 (about 350 mg/m2).

In a particular embodiment, a method of treating a subject with cancer includes intravenously administering to the subject in a single dose per three week period: paclitaxel in an amount of about 205 μmol/m2 (175 mg/m2); and Compound (1)or a pharmaceutically acceptable salt or solvate thereof in an amount of about 874 μmol/m2 (350 mg/m2), wherein the cancer is a soft tissue sarcomas other than GIST or metastatic melanoma.

In various embodiments, a pharmaceutical composition includes a pharmaceutically acceptable carrier or diluent; and a molar ratio of a bis(thiohydrazide amide) to a taxane between about 5.5:1 and about 5.9:1, wherein the bis(thiohydrazide amide) represented by Structural Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the molar ratio of the bis(thiohydrazide amide)

to the taxane is between about 5.6:1 and about 5.8:1, or more typically, about 5.7:1. In certain embodiments, the taxane is paclitaxel or a pharmaceutically acceptable salt or solvate thereof. In particular embodiments, the bis(thiohydrazide amide) is Compound (1).

In various embodiments, a pharmaceutical composition includes a pharmaceutically acceptable carrier or diluent; and a molar ratio of a bis(thiohydrazide amide) to a taxane between about 2.6:1 and about 3.0:1, wherein the bis(thiohydrazide amide) represented by Structural Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the molar ratio of the bis(thiohydrazide amide) to the taxane is between about 2.7:1 and about 2.9:1, or more typically, about 2.8:1. In certain embodiments, the taxane is paclitaxel or a pharmaceutically acceptable salt or solvate thereof. In particular embodiments, the bis(thiohydrazide amide) is Compound (1).

In various embodiments, a pharmaceutical composition includes a pharmaceutically acceptable carrier or diluent; and a molar ratio of a bis(thiohydrazide amide) to a taxane between about 4.1:1 and about 4.5:1, wherein the bis(thiohydrazide amide) represented by Structural Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the molar ratio of the bis(thiohydrazide amide) to the taxane is between about 4.2:1 and about 4.4:1, or more typically, about 4.3:1. In certain embodiments, the taxane is paclitaxel or a pharmaceutically acceptable salt or solvate thereof. In particular embodiments, the bis(thiohydrazide amide) is Compound (1).

In various embodiments, the invention includes the use of a bis(thiohydrazide amide) for the manufacture of medicament for treating cancer in combination with a taxane in a molar ratio of bis(thiohydrazide amide) to taxane between about 5.5:1 and about 5.9:1, typically between about 5.6:1 and about 5.8:1, more typically about 5.7:1, wherein the bis(thiohydrazide amide) is represented by Structural Formula I. In some embodiments, the molar ratio of bis(thiohydrazide amide) to taxane can be between about 2.6:1 and about 3.0:1, typically between about 2.7:1 and about 2.9:1, more typically about 2.8:1. In some embodiments, the molar ratio of bis(thiohydrazide amide)

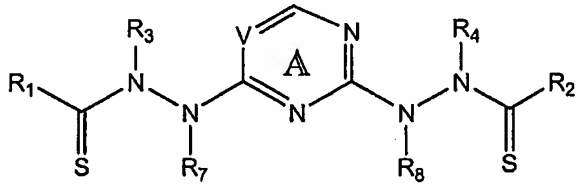
to taxane can be between about 4.1:1 and about 4.5:1, typically between about 4.2:1 and about 4.4:1, more typically about 4.3:1.

In various embodiments, the invention includes the use of a bis(thiohydrazide amide) and taxane for the manufacture of medicament for treating cancer in a molar ratio of bis(thiohydrazide amide) to taxane between about 5.5:1 and about 5.9:1, typically between about 5.6:1 and about 5.8:1, more typically about 5.7:1, wherein the bis(thiohydrazide amide) is represented by Structural Formula I. In some embodiments, the molar ratio of bis(thiohydrazide amide) to taxane can be between about 2.6:1 and about 3.0:1, typically between about 2.7:1 and about 2.9:1, more typically about 2.8:1. In some embodiments, the molar ratio of bis(thiohydrazide amide) to taxane can be between about 4.1:1 and about 4.5:1, typically between about 4.2:1 and about 4.4:1, more typically about 4.3:1.

The bis(thiohydrazide amides) employed in the disclosed invention are represented by Structural Formula I, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, Y in Structural Formula I is a covalent bond, $-C(R_5R_6)-$, $-(CH_2CH_2)-$, trans-(CH=CH)-, cis-(CH=CH)- or –(C≡C)- group, preferably $-C(R_5R_6)-$. R_1-R_4 are as described above for Structural Formula I. R_5 and R_6 are each independently -H, an aliphatic or substituted aliphatic group, or R_5 is -H and R_6 is an optionally substituted aryl group, or, R_5 and R_6, taken together, are an optionally substituted C2-C6 alkylene group. The pharmaceutically acceptable cation is as described in detail below.

In specific embodiments, Y taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group. In this instance, certain bis(thiohydrazide amides) are represented by Structural Formula III:



II

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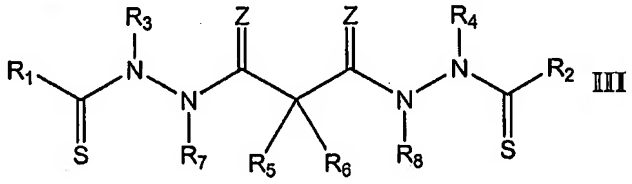
wherein Ring A is substituted or unsubstituted and V is –CH- or –N-. The other variables in Structural Formula II are as described herein for Structural Formula I or III.

In particular embodiments, the bis(thiohydrazide amides) are represented by Structural Formula III:



III

R_1-R_8 and the pharmaceutically acceptable cation are as described above for Structural Formula I.

In Structural Formulas I-III, R_1 and R_2 are the same or different and/or R_3 and R_4 are the same or different; preferably, R_1 and R_2 are the same and R_3 and R_4 are the same. In Structural Formulas I and III, Z is preferably O. Typically in Structural Formulas II and III, Z is O; R_1 and R_2 are the same; and R_3 and R_4 are the same. More preferably, Z is O; R_1 and R_2 are the same; R_3 and R_4 are the same, and R_7 and R_8 are the same.

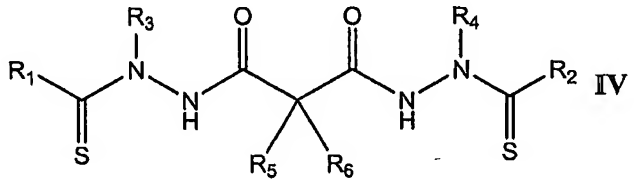
In other embodiments, the bis(thiohydrazide amides) are represented by Structural Formula III: R_1 and R_2 are each an optionally substituted aryl group, preferably an optionally substituted phenyl group; R_3 and R_4 are each an optionally substituted aliphatic group, preferably an alkyl group, more preferably, methyl or ethyl; and R_5 and R_6 are as described above, but R_5 is preferably –H and R_6 is preferably –H, an aliphatic or substituted aliphatic group.

Alternatively, R_1 and R_2 are each an optionally substituted aryl group; R_3 and R_4 are each an optionally substituted aliphatic group; R_5 is -H; and R_6 is -H, an aliphatic or substituted aliphatic group. Preferably, R_1 and R_2 are each an optionally substituted aryl group; R_3 and R_4 are each an alkyl group; and R_5 is -H and R_6 is -H or methyl. Even more preferably, R_1 and R_2 are each an optionally substituted phenyl group; R_3 and R_4 are each methyl or ethyl; and R_5 is -H and R_6 is -H or methyl. Suitable substituents for an aryl group represented by R_1 and R_2 and an aliphatic group represented by R_3, R_4 and R_6 are as described below for aryl and aliphatic groups.

In another embodiment, the bis(thiohydrazide amides) are represented by Structural Formula III: R_1 and R_2 are each an optionally substituted aliphatic group, preferably a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group, more preferably cyclopropyl or 1-methylcyclopropyl; R_3 and R_4 are as described above for Structural Formula I, preferably both an optionally substituted alkyl group; and R_5 and R_6 are as described above, but R_5 is preferably –H and R_6 is preferably –H, an aliphatic or substituted aliphatic group, more preferably –H or methyl.

Alternatively, the bis(thiohydrazide amides) are represented by Structural Formula III: R_1 and R_2 are each an optionally substituted aliphatic group; R_3 and R_4 are as described above for Structural Formula I, preferably both an optionally substituted alkyl group; and R_5 is –H and R_6 is –H or an optionally substituted aliphatic group. Preferably, R_1 and R_2 are both a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group; R_3 and R_4 are both as described above for Structural Formula I, preferably an alkyl group; and R_5 is –H and R_6 is –H or an aliphatic or substituted aliphatic group. More preferably, R_1 and R_2 are both a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group; R_3 and R_4 are both an alkyl group; and R_5 is –H and R_6 is –H or methyl. Even more preferably, R_1 and R_2 are both cyclopropyl or 1-methylcyclopropyl; R_3 and R_4 are both an alkyl group, preferably methyl or ethyl; and R_5 is –H and R_6 is –H or methyl.

In specific embodiments, the bis(thiohydrazide amides) are represented by Structural Formula IV:



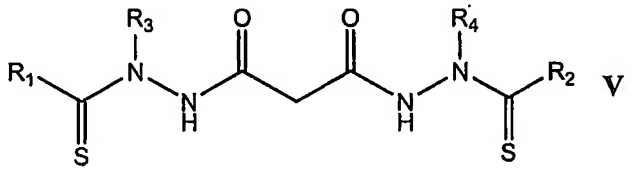
IV

wherein: R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 4-cyanophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 4-methoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both ethyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both 4-cyanophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 3-cyanophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 3-fluorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 4-chlorophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 3-methoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,3-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,3-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2,5-difluorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-difluorophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2,5-dichlorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethylphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is methyl and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is ethyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is *n*-propyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both methyl; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 is methyl, R_4 is ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2-phenylcyclopropyl,

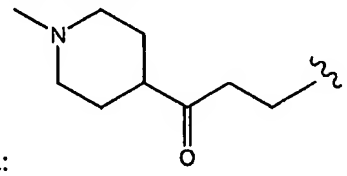
R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-phenylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclobutyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopentyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclohexyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclohexyl, R_3 and R_4 are both phenyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both *t*-butyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both phenyl, and R_5 and R_6 are both -H; R_1 and R_2 are both *t*-butyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are ethyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; or R_1 and R_2 are both *n*-propyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H.

In specific embodiments, the bis(thiohydrazide amides) are represented by Structural Formula V:



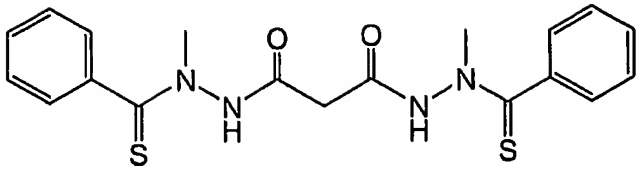
V

wherein: R_1 and R_2 are both phenyl, and R_3 and R_4 are both *o*-CH_3-phenyl; R_1 and R_2 are both *o*-$CH_3C(O)O$-phenyl, and R_3 and R_4 are phenyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both *n*-propyl; R_1 and R_2 are both *p*-cyanophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both *p*-nitro phenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both *n*-butyl; R_1 and R_2 are both *p*-chlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-nitrophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-cyanophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-fluorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-furanyl, and R_3 and R_4 are both phenyl; R_1 and R_2 are both 2-methoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-methoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,3-dimethoxyphenyl, and R_3 and R_4

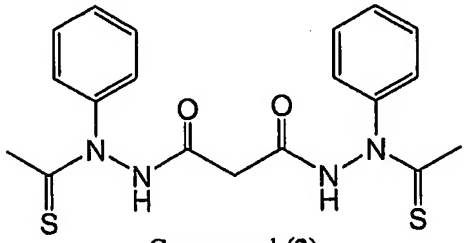
are both methyl; R_1 and R_2 are both 2-methoxy-5-chlorophenyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both 2,5-difluorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dichlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dimethylphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methoxy-5-chlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3,6-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both 2-ethylphenyl; R_1 and R_2 are both 2-methyl-5-pyridyl, and R_3 and R_4 are both methyl; or R_1 is phenyl; R_2 is 2,5-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *p*-CF_3-phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *o*-CH_3-phenyl; R_1 and R_2 are both $-(CH_2)_3COOH$; and R_3 and R_4 are both phenyl; R_1 and R_2 are both represented by the following structural formula: 

,and R_3 and R_4 are both phenyl; R_1 and R_2 are both *n*-butyl, and R_3 and R_4 are both phenyl; R_1 and R_2 are both *n*-pentyl, R_3 and R_4 are both phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2-pyridyl; R_1 and R_2 are both cyclohexyl, and R_3 and R_4 are both phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2-ethylphenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2,6-dichlorophenyl; R_1-R_4 are all methyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *t*-butyl; R_1 and R_2 are both ethyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both *t*-butyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopropyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both 1-methylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 1-phenylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-phenylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclobutyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopentyl, and R_3 and R_4 are both methyl; R_1 is cyclopropyl, R_2 is phenyl, and R_3 and R_4 are both methyl.

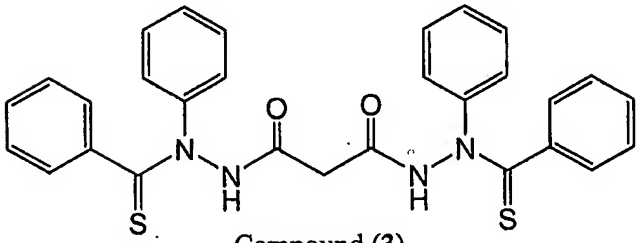
Preferred examples of bis(thiohydrazide amides) include Compounds **(1)-(18)** and pharmaceutically acceptable salts and solvates thereof:



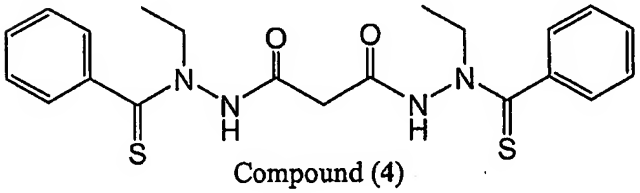
Compound (1) ;



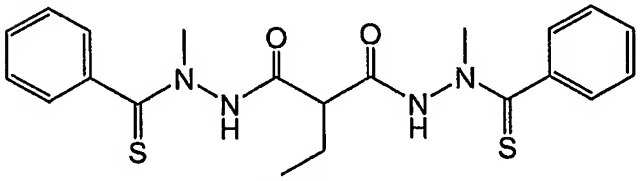
Compound (2) ;



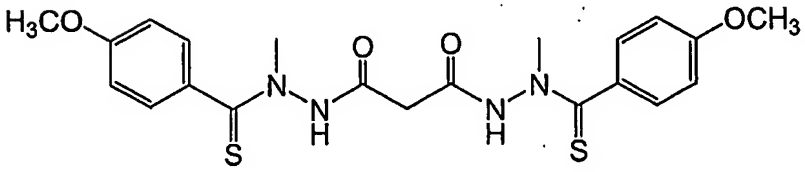
Compound (3) ;



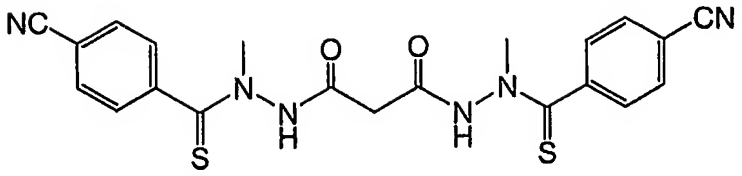
Compound (4) ;



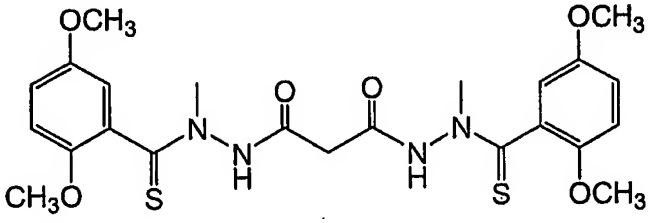
Compound (5) ;



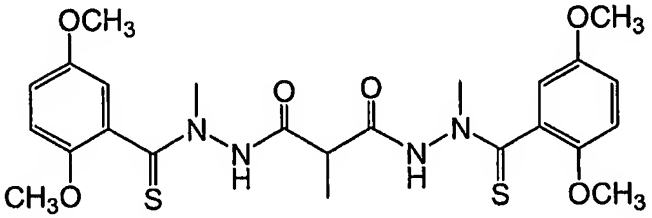
Compound (6) ;



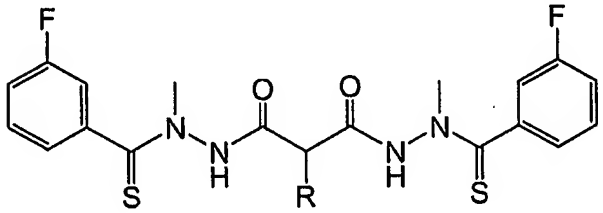
Compound (7) ;



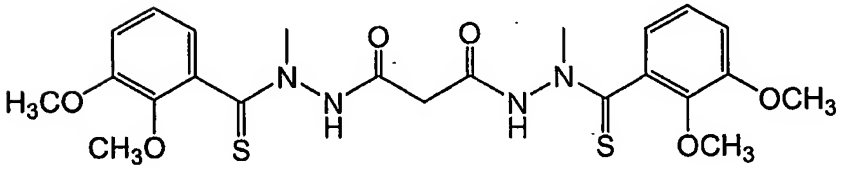
Compound (8) ;



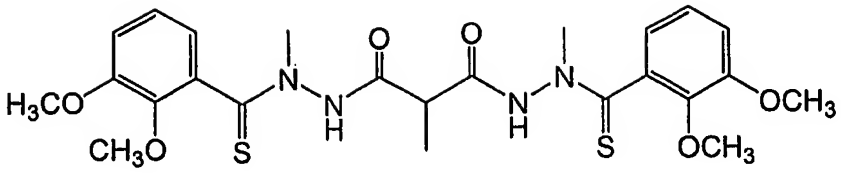
Compound (9) ;



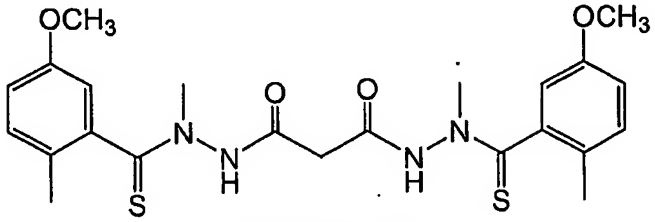
Compound (10) ;



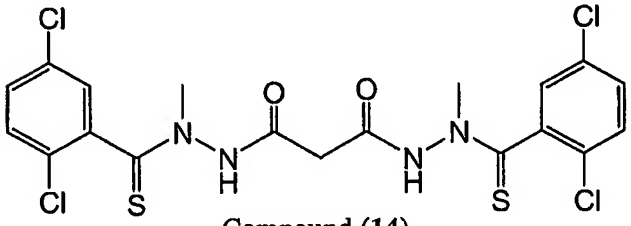
Compound (11) ;



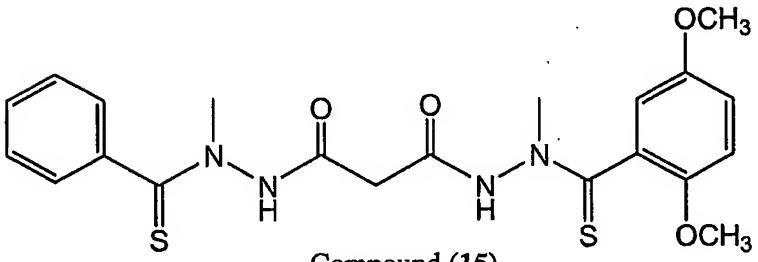
Compound (**12**) ;



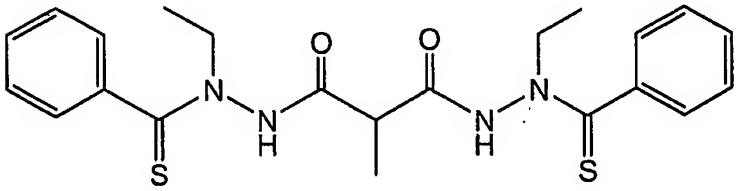
Compound (**13**) ;



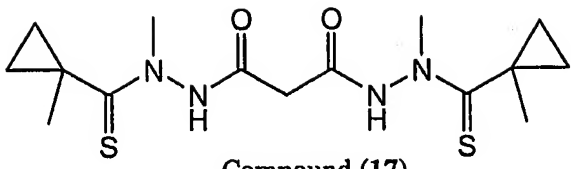
Compound (**14**) ;



Compound (**15**) ;

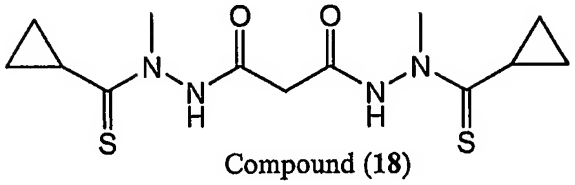


Compound (**16**) ;



Compound (17)

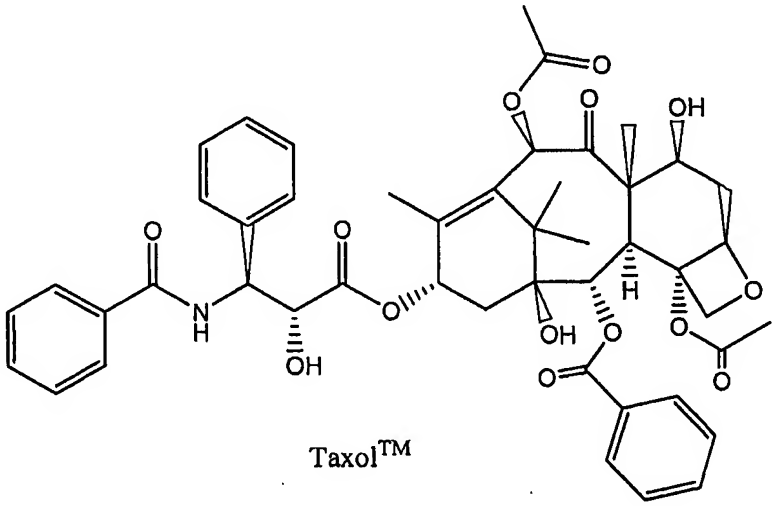
; and



Compound (18)

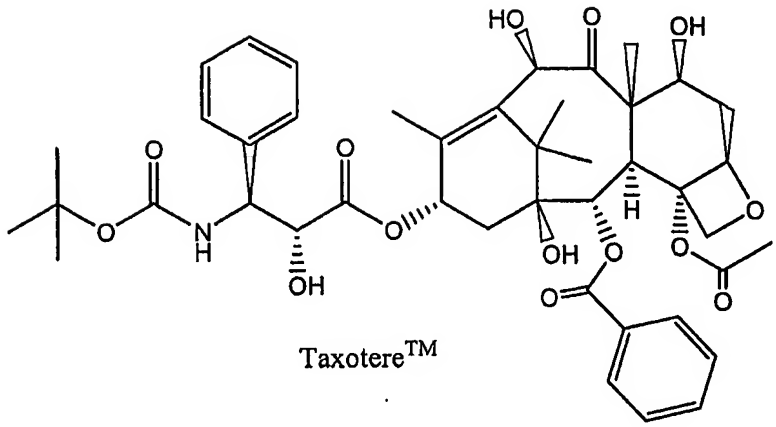
Particular examples of bis(thiohydrazide amides) include Compounds (1), (17), and (18) and pharmaceutically acceptable salts and solvates thereof.

The taxanes employed employed in the disclosed invention include Taxol™ and Taxol™ analogs. Taxol™ or "paclitaxel" is a well-known anti-cancer drug which can act by enhancing and stabilizing microtubule formation. Thus, the term "Taxol™ analog" is defined herein to mean a compound which has the basic Taxol™ skeleton and which stabilizes microtubule formation. Many analogs of Taxol™ are known, including Taxotere™, also referred to as "docetaxol". Taxol™ and Taxotere™ have the respective structural formulas:



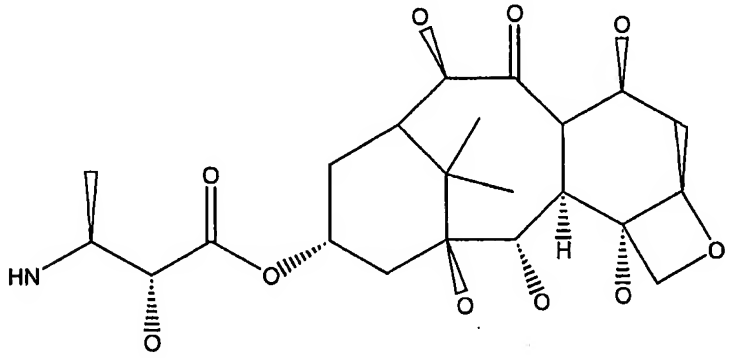
Taxol™

; and



Taxotere™

The taxanes employed in the disclosed invention have the basic taxane skeleton as a common structure feature shown below in Structural Formula VI:



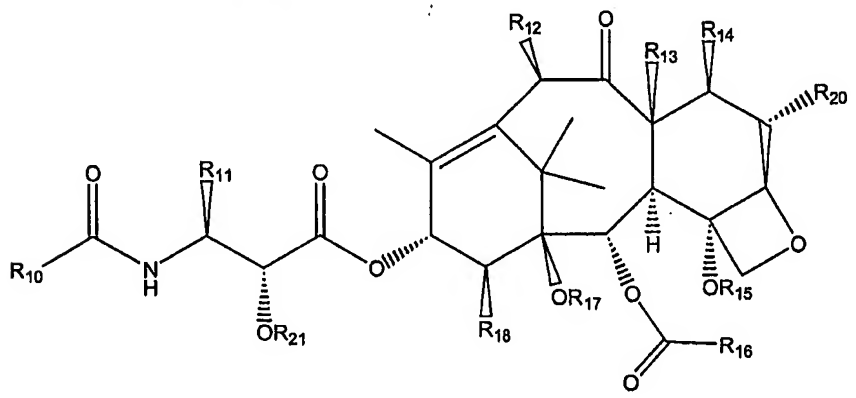
VI

Double bonds have been omitted from the cyclohexane rings in the taxane skeleton represented by Structural Formula VI. It is to be understood that the basic taxane skeleton can include zero or one double bond in one or both cyclohexane rings, as indicated in the Taxol™ analogs and Structural Formulas VII and VIII below. A number of atoms have also been omitted from Structural Formula VI to indicate sites in which structural variation commonly occurs among Taxol™ analogs.

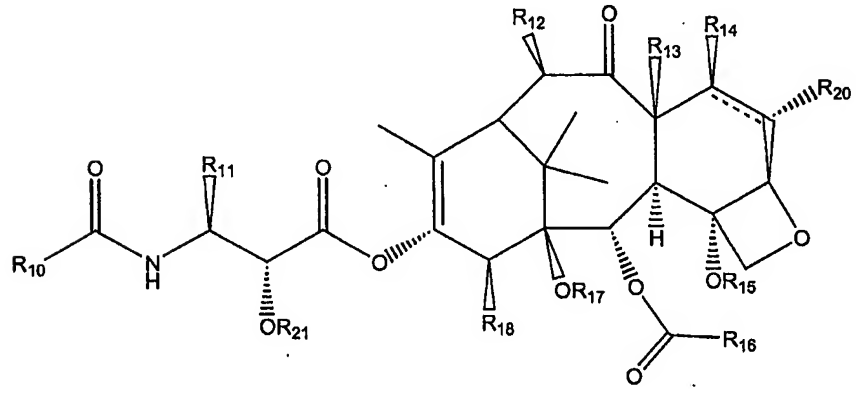
A wide variety of substituents can decorate the taxane skeleton without adversely affecting biological activity. Also, zero, one or both of the cyclohexane rings of a Taxol™ analog can have a double bond at the indicated positions. For example, substitution on the taxane skeleton with simply an oxygen atom indicates that hydroxyl, acyl, alkoxy or other oxygen-bearing substituent is commonly found at the site. It is to be understood that these and other substitutions on the taxane skeleton can be made

without losing the ability to enhance and stabilize microtubule formation. Thus, the term "Taxol™ analog" is defined herein to mean a compound which has the basic Taxol™ skeleton and which stabilizes microtubule formation. The term taxane is defined herein to include compounds such as Taxol™ and the "Taxol™ analogs" described herein, or a pharmaceutically acceptable salt or solvate thereof.

Typically, the taxanes employed in the disclosed invention are represented by Structural Formula VII or VIII:



VII



VIII

R_{10} is an optionally substituted lower alkyl group, an optionally substituted phenyl group, $-SR_{19}$, $-NHR_{19}$ or $-OR_{19}$.

R_{11} is an optionally substituted lower alkyl group, an optionally substituted aryl group .

R_{12} is -H, -OH, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, -O-C(O)-(lower alkyl), -O-C(O)-(substituted lower alkyl), -O-CH_2-O-(lower alkyl) -S-CH_2-O-(lower alkyl).

R_{13} is -H, -CH_3, or, taken together with R_{14}, -CH_2-.

R_{14} is -H, -OH, lower alkoxy, -O-C(O)-(lower alkyl), substituted lower alkoxy, -O-C(O)-(substituted lower alkyl), -O-CH_2-O-P(O)$(OH)_2$, -O-CH_2-O-(lower alkyl), -O-CH_2-S-(lower alkyl) or, taken together with R_{20}, a double bond.

R_{15} -H, lower acyl, lower alkyl, substituted lower alkyl, alkoxymethyl, alkthiomethyl, -OC(O)-O(lower alkyl), -OC(O)-O(substituted lower alkyl), -OC(O)-NH(lower alkyl) or -OC(O)-NH(substituted lower alkyl).

R_{16} is phenyl or substituted phenyl.

R_{17} is -H, lower acyl, substituted lower acyl, lower alkyl, substituted, lower alkyl, (lower alkoxy)methyl or (lower alkyl)thiomethyl.

R_{18} -H, -CH_3 or, taken together with R_{17} and the carbon atoms to which R_{17} and R_{18} are bonded, a five or six membered a non-aromatic heterocyclic ring.

R_{19} is an optionally substituted lower alkyl group, an optionally substituted phenyl group.

R_{20} is -H or a halogen.

R_{21} is -H, lower alkyl, substituted lower alkyl, lower acyl or substituted lower acyl.

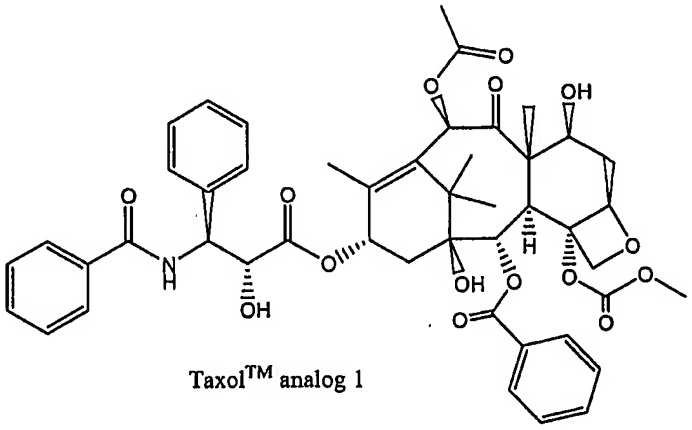
Preferably, the variables in Structural Formulas **VII** and **VIII** are defined as follows: R_{10} is phenyl, *tert*-butoxy, -S-CH_2-CH-$(CH_3)_2$, -S-CH$(CH_3)_3$, -S-$(CH_2)_3CH_3$, -O-CH$(CH_3)_3$, -NH-CH$(CH_3)_3$, -CH=C$(CH_3)_2$ or *para*-chlorophenyl; R_{11} is phenyl, $(CH_3)_2CHCH_2$-, -2-furanyl, cyclopropyl or *para*-toluyl; R_{12} is -H, -OH, CH_3CO- or -$(CH_2)_2$-*N*-morpholino; R_{13} is methyl, or, R_{13} and R_{14}, taken together, are -CH_2-;

R_{14} is -H, -CH_2SCH_3 or -CH_2-O-P(O)$(OH)_2$; R_{15} is CH_3CO-;

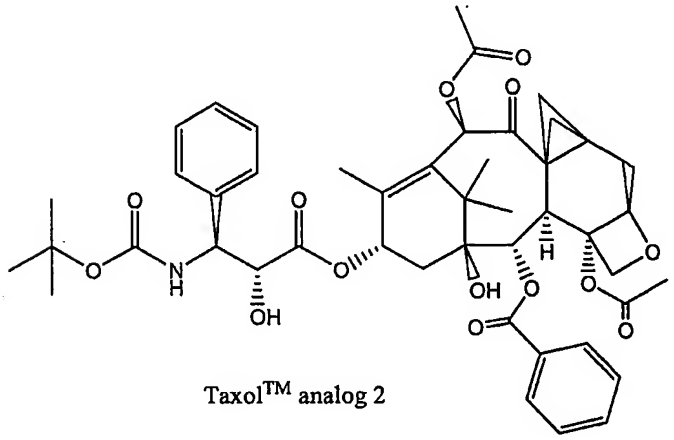
R_{16} is phenyl; R_{17} -H, or, R_{17} and R_{18}, taken together, are -O-CO-O-;

R_{18} is -H; R_{20} is -H or -F; and R_{21} is -H, -C(O)-CHBr-$(CH_2)_{13}$-CH_3 or -C(O)-$(CH_2)_{14}$-CH_3; -C(O)-CH_2-CH(OH)-COOH, -C(O)-CH_2-O-C(O)-$CH_2CH(NH_2)$-$CONH_2$, -C(O)-CH_2-O--$CH_2CH_2OCH_3$ or -C(O)-O-C(O)-CH_2CH_3.

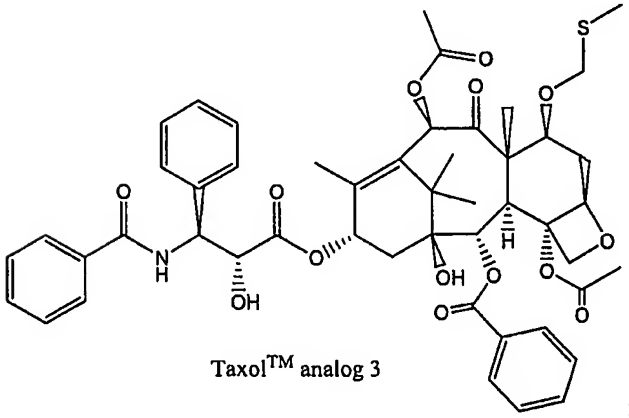
Specific examples of Taxol™ analogs include the following compounds:



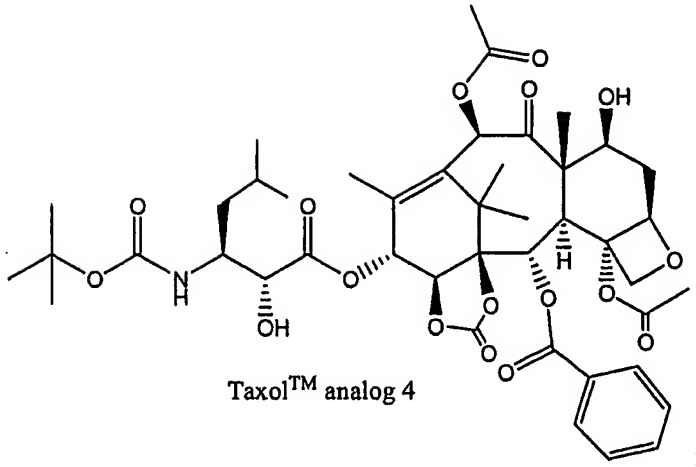
Taxol™ analog 1 ;



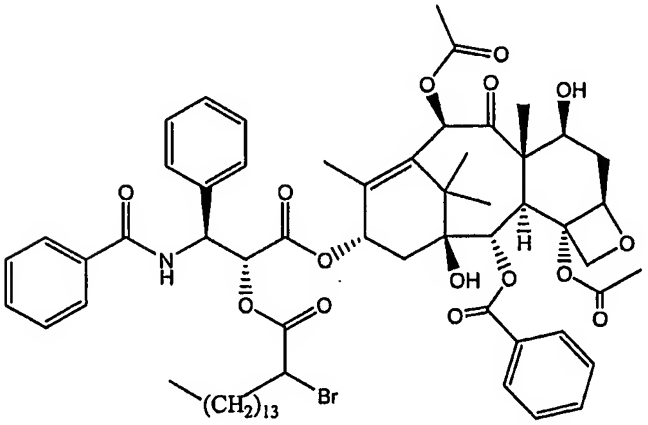
Taxol™ analog 2 ;



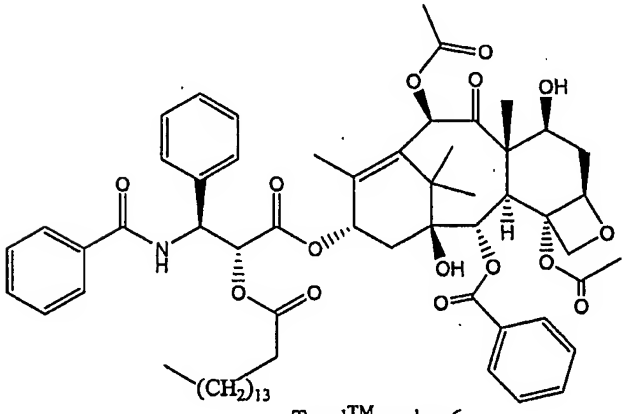
Taxol™ analog 3 ;



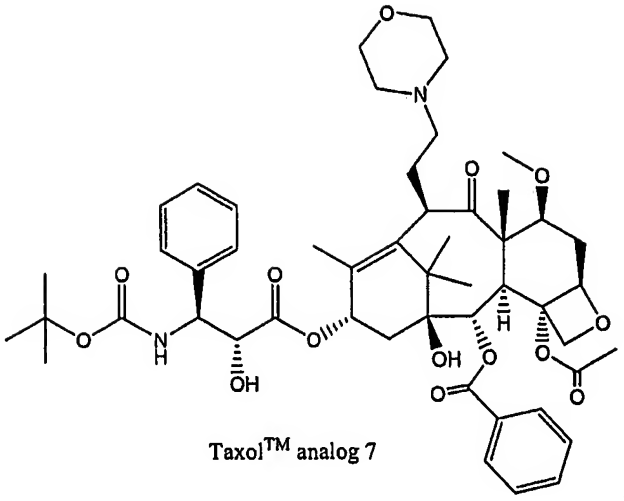
Taxol™ analog 4 ;



Taxol™ analog 5 ;



Taxol™ analog 6 ;



Taxol™ analog 7

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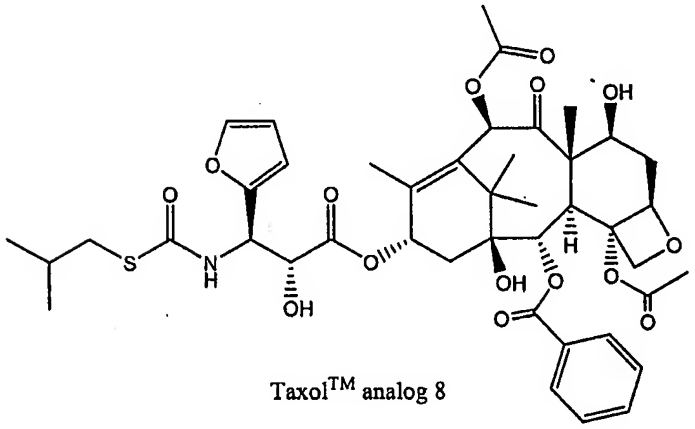

Taxol™ analog 8

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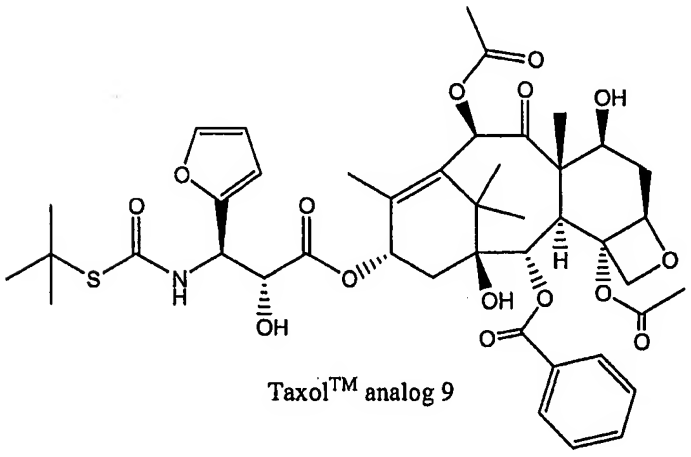

Taxol™ analog 9

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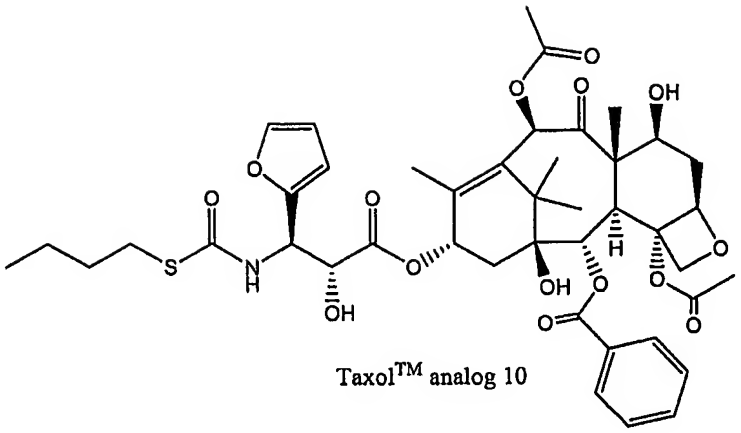
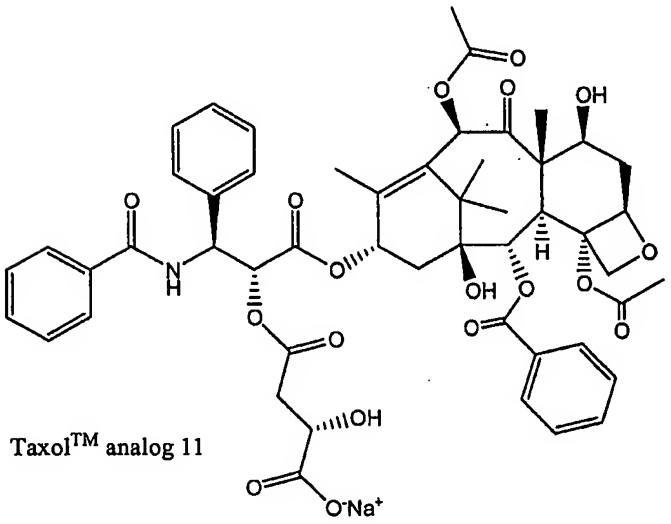
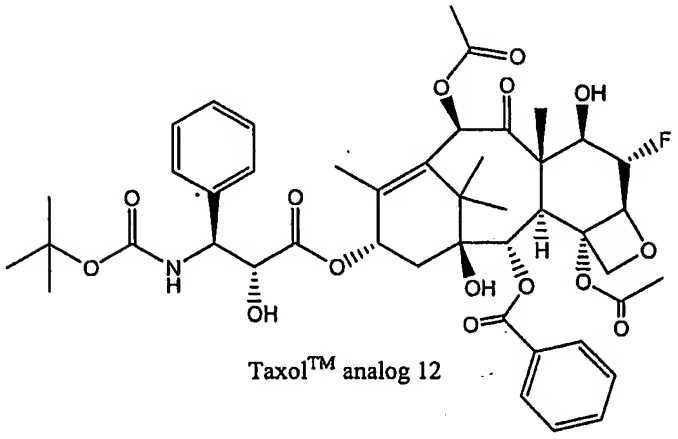


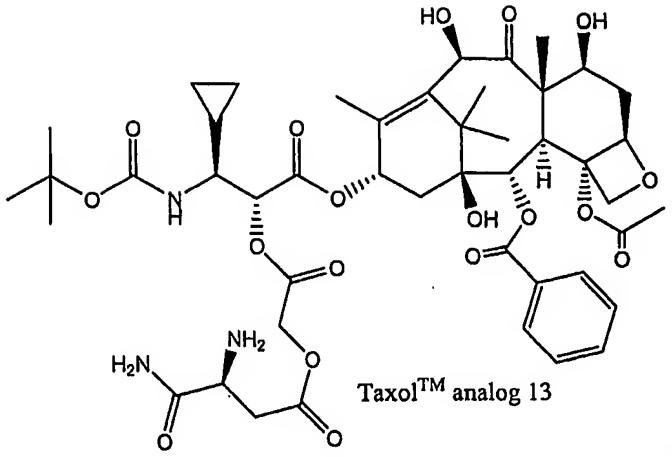
Taxol™ analog 10 ;



Taxol™ analog 11 ;



Taxol™ analog 12 ;



Taxol™ analog 13

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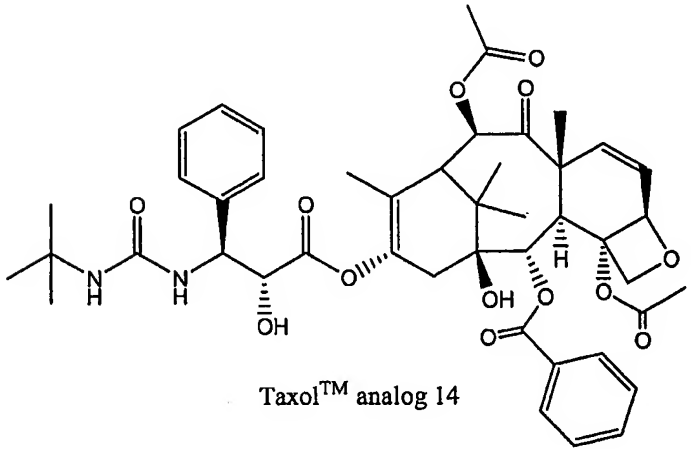

Taxol™ analog 14

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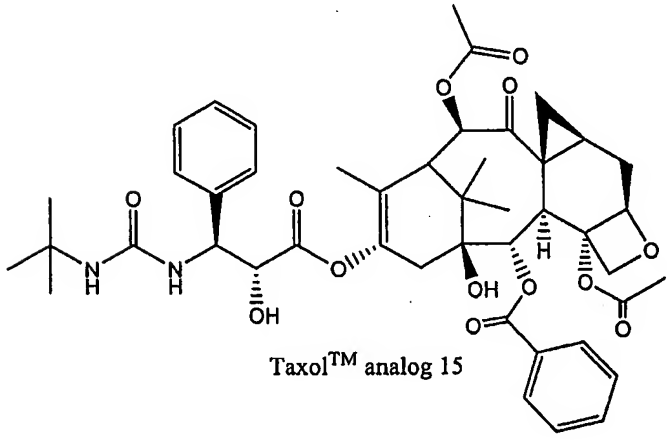

Taxol™ analog 15

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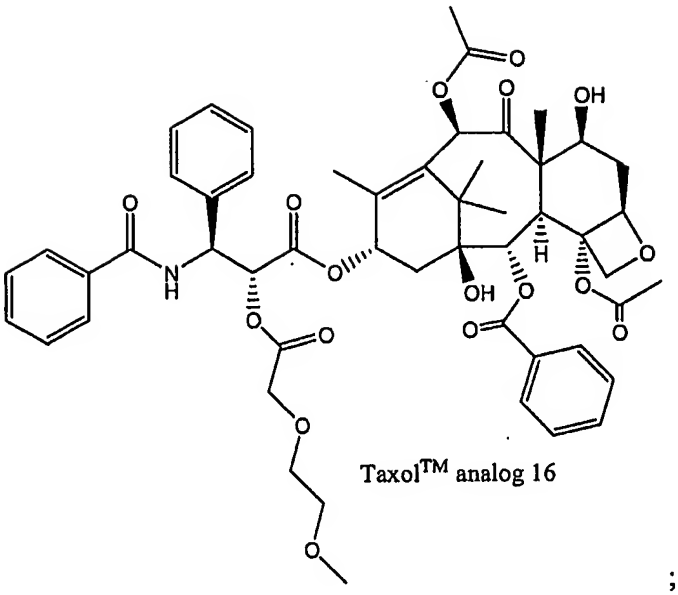

Taxol™ analog 16

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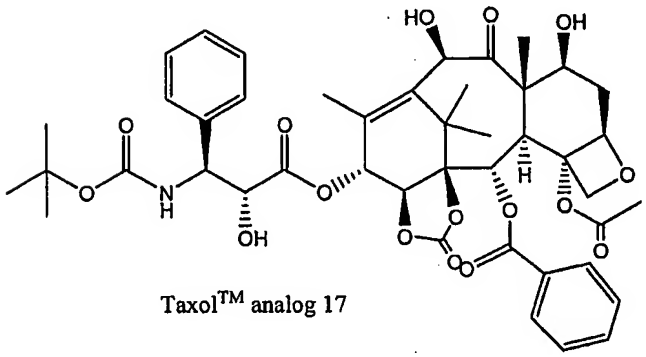

Taxol™ analog 17

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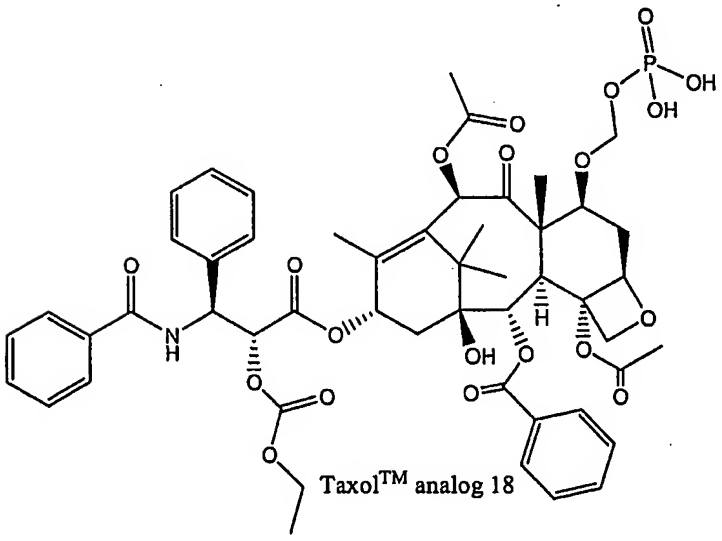

Taxol™ analog 18

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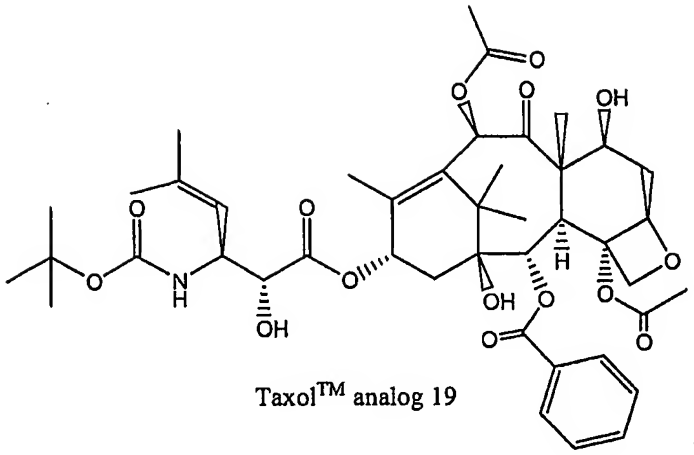

Taxol™ analog 19

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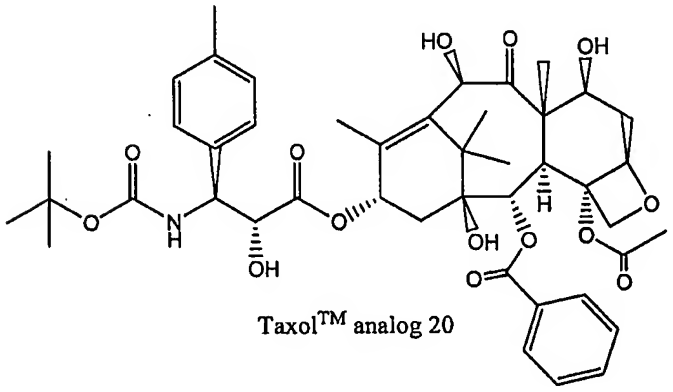

Taxol™ analog 20

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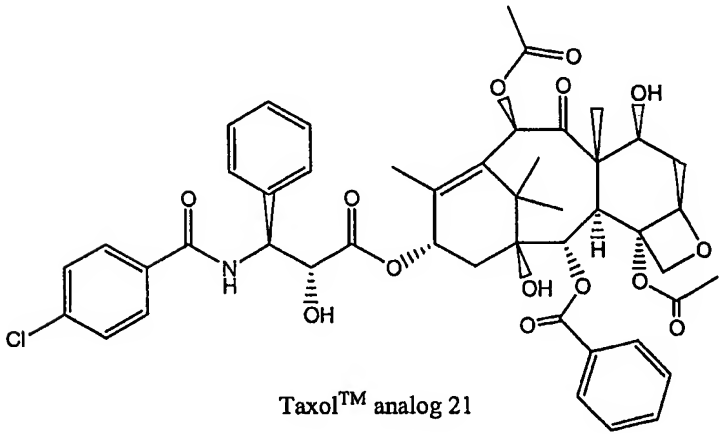
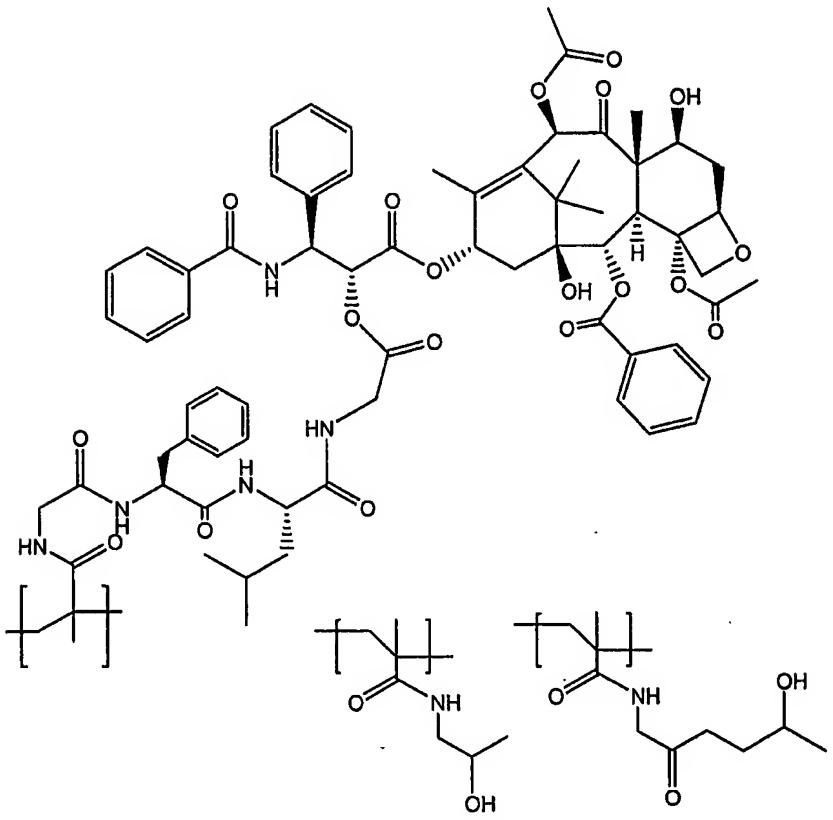


Taxol™ analog 21

A Taxol™ analog can also be bonded to or be pendent from a pharmaceutically acceptable polymer, such as a polyacrylamide. One example of a polymer of this type is Taxol™ analog 22, below, which has the structure of a polymer comprising a taxol analog group pendent from the polymer backbone. The polymer is a terpolymer of the

three monomer units shown. The term "Taxol™ analog", as it is used herein, includes such polymers.



Taxol™ analog 22

A "straight chained hydrocarbyl group" is an alkylene group, *i.e.*, $-(CH_2)_y-$, with one, or more (preferably one) internal methylene groups optionally replaced with a linkage group. y is a positive integer (*e.g.*, between 1 and 10), preferably between 1 and 6 and more preferably 1 or 2. A "linkage group" refers to a functional group which replaces a methylene in a straight chained hydrocarbyl. Examples of suitable linkage groups include a ketone (-C(O)-), alkene, alkyne, phenylene, ether (-O-), thioether (-S-), or amine ($-N(R^a)-$), wherein R^a is defined below. A preferred linkage group is $-C(R_5R_6)-$, wherein R_5 and R_6 are defined above. Suitable substituents for an alkylene group and a hydrocarbyl group are those which do not substantially interfere with the

anti-cancer activity of the bis(thiohydrazide) amides and taxanes. R_5 and R_6 are preferred substituents for an alkylene or hydrocarbyl group represented by Y.

An aliphatic group is a straight chained, branched or cyclic non-aromatic hydrocarbon which is completely saturated or which contains one or more units of unsaturation. Typically, a straight chained or branched aliphatic group has from 1 to about 20 carbon atoms, preferably from 1 to about 10, and a cyclic aliphatic group has from 3 to about 10 carbon atoms, preferably from 3 to about 8. An aliphatic group is preferably a straight chained or branched alkyl group, *e.g.*, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, pentyl or octyl, or a cycloalkyl group with 3 to about 8 carbon atoms. A C1-C20 straight chained or branched alkyl group or a C3-C8 cyclic alkyl group is also referred to as a "lower alkyl" group.

The term "aromatic group" may be used interchangeably with "aryl," "aryl ring," "aromatic ring," "aryl group" and "aromatic group." Aromatic groups include carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl, and heteroaryl groups such as imidazolyl, thienyl, furanyl, pyridyl, pyrimidyl, pyranyl, pyrazolyl, pyrroyl, pyrazinyl, thiazole, oxazolyl, and tetrazole. The term "heteroaryl group" may be used interchangeably with "heteroaryl," "heteroaryl ring," "heteroaromatic ring" and "heteroaromatic group." The term "heteroaryl," as used herein, means a mono-or multi-cyclic aromatic heterocycle which comprise at least one heteroatom such as nitrogen, sulfur and oxygen, but may include 1, 2, 3 or 4 heteroatoms per ring. Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Examples include benzothienyl, benzofuranyl, indolyl, quinolinyl, benzothiazole, benzooxazole, benzimidazole, quinolinyl, isoquinolinyl and isoindolyl.

The term "arylene" refers to an aryl group which is connected to the remainder of the molecule by two other bonds. By way of example, the structure of a 1,4-phenylene group is shown below:

Substituents for an arylene group are as described below for an aryl group.

Non-aromatic heterocyclic rings are non-aromatic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered. Examples include tetrahydrofuranyl, tetrahydrothiophenyl, morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, and thiazolidinyl.

Suitable substituents on an aliphatic group (including an alkylene group), non-aromatic heterocyclic group, benzylic or aryl group (carbocyclic and heteroaryl) are those which do not substantially interfere with the anti-cancer activity of the bis(thiohydrazide) amides and taxanes.. A substituent substantially interferes with anti-cancer activity when the anti-cancer activity is reduced by more than about 50% in a compound with the substituent compared with a compound without the substituent. Examples of suitable substituents include $-R^a$, -OH, -Br, -Cl, -I, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NR^cCOR^a$, $-NHCONH_2$, $-NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$, $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$, $-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$. R^a-R^d are each independently an alkyl group, aromatic group, non-aromatic heterocyclic group or $-N(R^aR^b)$, taken together, form an optionally substituted non-aromatic heterocyclic group. The alkyl, aromatic and non-aromatic heterocyclic group represented by R^a-R^d and the non-aromatic heterocyclic group represented by $-N(R^aR^b)$ are each optionally and independently substituted with one or more groups represented by $R^{\#}$.

$R^{\#}$ is R^+, $-OR^+$, -O(haloalkyl), $-SR^+$, $-NO_2$, -CN, -NCS, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$,

$-C(=S)N(R^+)_2$, or $-C(=NH)-N(R^+)_2$.

R^+ is –H, a C1-C4 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, $-NO_2$, amine, alkylamine or dialkylamine. Optionally, the group $-N(R^+)_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups represented by R^+ and $-N(R^+)_2$ that comprise a secondary ring amine are optionally acylated or alkylated.

Preferred substituents for a phenyl group, including phenyl groups represented by R_1-R_4, include C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, phenyl, benzyl, pyridyl, -OH, $-NH_2$, -F, -Cl, -Br, -I, $-NO_2$ or -CN.

Preferred substituents for an aliphatic group, including aliphatic groups represented by R_1-R_4, include C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, phenyl, benzyl, pyridyl, -OH, $-NH_2$, -F, -Cl, -Br, -I, $-NO_2$ or -CN.

Preferred substituents for a cycloalkyl group, including cycloalkyl groups represented by R_1 and R_2, are alkyl groups, such as a methyl or ethyl groups.

Also included in the present invention are pharmaceutically acceptable salts of the bis(thiohydrazide) amides and taxanes employed herein. These compounds can have one or more sufficiently acidic protons that can react with a suitable organic or inorganic base to form a base addition salt. Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases such as alkoxides, alkyl amides, alkyl and aryl amines, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like.

For example, pharmaceutically acceptable salts of bis(thiohydrazide) amides and taxanes employed herein (*e.g.*, those represented by Structural Formulas **I-VI**, Compounds **1-18**, and Taxol™ analogs **1-22**) are those formed by the reaction of the compound with one equivalent of a suitable base to form a monovalent salt (*i.e.*, the compound has single negative charge that is balanced by a pharmaceutically acceptable counter cation, *e.g.*, a monovalent cation) or with two equivalents of a suitable base to form a divalent salt (*e.g.*, the compound has a two-electron negative charge that is

balanced by two pharmaceutically acceptable counter cations, *e.g.*, two pharmaceutically acceptable monovalent cations or a single pharmaceutically acceptable divalent cation). Divalent salts of the bis(thiohydrazide amides) are preferred. "Pharmaceutically acceptable" means that the cation is suitable for administration to a subject. Examples include Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+} and NR_4^+, wherein each R is independently hydrogen, an optionally substituted aliphatic group (*e.g.*, a hydroxyalkyl group, aminoalkyl group or ammoniumalkyl group) or optionally substituted aryl group, or two R groups, taken together, form an optionally substituted non-aromatic heterocyclic ring optionally fused to an aromatic ring. Generally, the pharmaceutically acceptable cation is Li^+, Na^+, K^+, $NH_3(C_2H_5OH)^+$ or $N(CH_3)_3(C_2H_5OH)^+$, and more typically, the salt is a disodium or dipotassium salt, preferably the disodium salt.

Bis(thiohydrazide) amides and taxanes employed herein having a sufficiently basic group, such as an amine can react with an organic or inorganic acid to form an acid addition salt. Acids commonly employed to form acid addition salts from compounds with basic groups are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like.

Particular salts of the bis(thiohydrazide amide) compounds described herein can be prepared according to methods described in copending, co-owned Patent Application Serial No. 60/582,596, filed June 23, 2004.

The neutral bis(thiohydrazide) amides can be prepared according to methods described in U.S. Patent Nos. 6,800,660, and 6,762,204, both entitled "Synthesis of Taxol Enhancers" and also according to methods described in the co-pending and co-owned U.S. Pat. Appl. Ser. Nos. 10/345,885 filed January 15, 2003, and 10/758,589, January 15, 2004. The entire teachings of each document referred to in this application is expressly incorporated herein by reference.

It will also be understood that certain compounds employed in the invention may be obtained as different stereoisomers (*e.g.*, diastereomers and enantiomers) and that the invention includes all isomeric forms and racemic mixtures of the disclosed compounds and methods of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures. Stereoisomers can be separated and isolated using any suitable method, such as chromatography.

As used herein, a "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like).

The bis(thiohydrazide) amides and taxanes employed herein can be administered to a subject by any conventional method of drug administration for treatment of cancerous disorders, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. In specific embodiments, oral, parenteral, or local administration are preferred modes of administration for treatment of cancer. Preferably, the mode of administration is intravenous.

An effective amount of a bis(thio-hydrazide) amide or a taxane anticancer compound is a quantity in which anti-cancer effects are normally achieved. With respect to a particular compound in the method (e.g., the bis(thio-hydrazide) amide or the taxane anticancer compound), an "effective amount" is the quantity in which a

greater anti-cancer effect is achieved when the particular compound is co-administered with the other compounds in the method compared with when the particular compound is administered alone. The compounds of the method can be co-administered to the subject as part of the same pharmaceutical composition or, alternatively, as separate pharmaceutical compositions. When administered as separate pharmaceutical compositions, the compounds of the method can be administered simultaneously or at different times, provided that the enhancing effect of the compounds in combination is retained.

As used herein, "treating a subject with a cancer," or similar terms, includes achieving, partially or substantially, one or more of the following: arresting the growth or spread of a cancer, reducing the extent of a cancer (*e.g.*, reducing size of a tumor or reducing the number of affected sites), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components).

In various embodiments, cancer can include human sarcomas and carcinomas, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and

polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrobm's macroglobulinemia, and heavy chain disease.

In some embodiments, cancer can include leukemias e.g.,acute and/or chronic leukemias, e.g., lymphocytic leukemia (e.g., as exemplified by the p388 (murine) cell line), large granular lymphocytic leukemia, and lymphoblastic leukemia; T-cell leukemias, e.g., T-cell leukemia (e.g., as exemplified by the CEM, Jurkat, and HSB-2 (acute), YAC-1(murine) cell lines), T-lymphocytic leukemia, and T-lymphoblastic leukemia; B cell leukemia (e.g., as exemplified by the SB (acute) cell line), and B-lymphocytic leukemia; mixed cell leukemias, e.g., B and T cell leukemia and B and T lymphocytic leukemia; myeloid leukemias, e.g., granulocytic leukemia, myelocytic leukemia (e.g., as exemplified by the HL-60 (promyelocyte) cell line), and myelogenous leukemia (e.g., as exemplified by the K562(chronic)cell line); neutrophilic leukemia; eosinophilic leukemia; monocytic leukemia (e.g., as exemplified by the THP-1(acute) cell line); myelomonocytic leukemia; Naegeli-type myeloid leukemia; and nonlymphocytic leukemia. Other examples of leukemias are described in Chapter 60 of *The Chemotherapy Sourcebook*, Michael C. Perry Ed., Williams & Williams (1992) and Section 36 of *Holland Frie Cancer Medicine* 5th Ed., Bast et al. Eds., B.C. Decker Inc. (2000). The entire teachings of the preceding references are incorporated herein by reference.

In certain embodiments, cancer can include non-solid tumors such as multiple myeloma, T-leukemia (e.g., as exemplified by Jurkat and CEM cell lines); B-leukemia (e.g., as exemplified by the SB cell line); promyelocytes (e.g., as exemplified by the HL-60 cell line); uterine sarcoma (e.g., as exemplified by the MES-SA cell line); monocytic leukemia (e.g., as exemplified by the THP-1(acute) cell line); and lymphoma (e.g., as exemplified by the U937 cell line).

In some embodiments, cancer can include colon cancer, pancreatic cancer, melanoma, renal cancer, sarcoma, breast cancer, ovarian cancer, lung cancer, stomach cancer, bladder cancer and cervical cancer.

In some embodiments, the disclosed methods can be particularly effective at treating subjects whose cancer has become "multi-drug resistant". A cancer which initially responded to an anti-cancer drug becomes resistant to the anti-cancer drug

when the anti-cancer drug is no longer effective in treating the subject with the cancer. For example, many tumors can initially respond to treatment with an anti-cancer drug by decreasing in size or even going into remission, only to develop resistance to the drug. Drug resistant tumors are characterized by a resumption of their growth and/or reappearance after having seemingly gone into remission, despite the administration of increased dosages of the anti-cancer drug. Cancers that have developed resistance to two or more anti-cancer drugs are said to be "multi-drug resistant". For example, it is common for cancers to become resistant to three or more anti-cancer agents, often five or more anti-cancer agents and at times ten or more anti-cancer agents.

The bis(thiohydrazide) amides and taxanes employed herein can be administered to the subject in conjunction with an acceptable pharmaceutical carrier or diluent as part of a pharmaceutical composition for treatment cancer therapy. Formulation of the compound to be administered will vary according to the route of administration selected (*e.g.*, solution, emulsion, capsule, and the like). Suitable pharmaceutically acceptable carriers may contain inert ingredients which do not unduly inhibit the biological activity of the compounds. The pharmaceutically acceptable carriers should be biocompatible, *i.e.*, non-toxic, non-inflammatory, non-immunogenic and devoid of other undesired reactions upon the administration to a subject. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, *ibid.* Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

In certain embodiments, one or more compounds of the invention and one or more other the therapies (*e.g.*, prophylactic or therapeutic agents) are cyclically administered. Cycling therapy involves the administration of a first therapy (*e.g.*, a first prophylactic or therapeutic agents) for a period of time, followed by the administration of a second therapy (*e.g.*, a second prophylactic or therapeutic agents) for a period of time, followed by the administration of a third therapy (*e.g.*, a third prophylactic or

therapeutic agents) for a period of time and so forth, and repeating this sequential administration, *i.e.*, the cycle in order to reduce the development of resistance to one of the agents, to avoid or reduce the side effects of one of the agents, and/or to improve the efficacy of the treatment.

In various embodiments, the methods herein can include administration prior to or concurrently with the bis(thiohydrazide) amide/taxane combination, agents that can reduce acute irritation or allergic reaction to administration, e.g., an anti-inflammatory such as Decadron® (dexamethasone, e.g., 10 mg intravenously), an antihistamine such as Benadryl® (diphenhydramine, e.g., 50 mg intravenously), an antacid such as Zantac® (ranitidine hydrochloride, e.g., 50 mg intravenously), and the like.

EXEMPLIFICATION

Example 1: Measurement of Heat Shock Protein 70 (Hsp70)

Plasma Hsp70 was measured by a sandwich ELISA kit (Stressgen Bioreagents Victoria, British Columbia, CANADA) according to a modified protocol in house. In brief, Hsp70 in plasma specimens and serial concentrations of Hsp70 standard were captured onto 96-well plate on which anti-Hsp70 antibody was coated. Then captured Hsp70 was detected with a biotinylated anti-Hsp70 antibody followed by incubation with europium-conjugated streptavidin. After each incubation unbound materials were removed by washing. Finally, antibody-Hsp70 complex was measured by time resolved fluorometry of europium. Concentration of Hsp70 was calculated from a standard curve.

Example 2: Measurement of Natural Killer Cell Cytotoxic Activity

The following procedure can be employed to assay NK cell activity in a subject. The procedure is adapted from Kantakamalakul W, Jaroenpool J, Pattanapanyasat K. A novel enhanced green fluorescent protein (EGFP)-K562 flow cytometric method for measuring natural killer (NK) cell cytotoxic activity. J Immunol Methods. 2003 Jan 15; 272:189-197, the entire teachings of which are incorporated herein by reference.

Materials and methods: Human erythroleukaemic cell line, K562, was obtained from American Type Culture Collection (CCL-243, American Type Culture Collection, Manassas, VA), and cultured in RPMI-1640 medium (Cat#11875-093Gibco Invitrogen

Corp, Carlsbad, CA) supplemented with 10% heat inactivated fetal calf serum (Gibco), 2mM L-glutamin, 100 μg/ml streptomycin and 100 IU/ml penicillin at 37° C with 5% CO_2. K562 cells were transduced with retroviral vector which encode green fluorescent protein (eGFP). Stable cell line was selected with antibiotic, G418. About 99.6% G418 resistant cells were eGFP positive after section.

The subject's peripheral blood mononuclear cells (PBMCs) were prepared by clinical study sites and received in BD Vacutainer Cell Preparation Tube with sodium heparin (Product Number: 362753, Becton Dickinson, Franklin Lakes, NJ).

Two-fold serial dilution of 800 μl effector cells (patient's PBMC) starting at concentration of $1X10^6$ cells/mL were put into four individual polystyrene 12X75-mm tubes. Log phase growing target cells (K562/eGFP) were adjusted with growth medium (RPMI-1640) to a concentration of $1X10^5$ cells/mL and 100 μL targets then added into the tubes to provide effector/target (E/T) ratios of 80:1, 40:1, 20:1, 10:1. Effector cells alone and target cells alone were used as controls. All tubes were incubated at 37° C with 5% CO_2 for about 3.5 hr. Ten microliters of propidium iodide (PI) at a concentration of 1 mg/mL was added to each tube including effector and target control tubes and then incubated at room temperature for 15 min.

Cytotoxic activity was analyzed with a FACSCalibur flow cytometer (Becton Dickinson). Linear amplification of the forward and side scatter (FSC/SSC) signals, as well as logarithmic amplification of eGFP and PI emission in green and red fluorescence were obtained. Ten thousand events per sample tube with no gating for acquisition were collected for analysis. Data analysis for two-parameter dot plots for eGFP versus PI was performed using CELLQuest (Becton Dickinson Biosciences) software to enumerate live and dead target cells. Debris and dead cells were excluded by setting a threshold of forward light scatter.

Example 3: The Disclosed Combination Therapy Induces Hsp70

A Phase I trial was conducted for combined administration of a bis(thio-hydrazide) amide (Compound (**1**)) and a taxane (paclitaxel) to human subjects with various advanced solid tumors. Compound (**1**) and paclitaxel were co-administered intravenously over 3 hours every 3 weeks. Starting doses were 44

milligrams/meter^2 (mg/m2, or 110 micromoles/meter^2 (μmol/m2)) Compound (1) and 135 mg/m2 (158 μmol/m2) paclitaxel . Paclitaxel was then increased to 175 mg/m2 (205 μmol/m2), followed by escalation of Compound (1) to establish the maximum tolerated dose based on first cycle toxicity in 3 to 6 patients at each dose level. Pharmacokinetic (PK) studies were performed during cycle 1 using liquid chromatography/mass spectrometry (LC/MS) to measure both compounds in plasma. Heat shock protein 70 (Hsp70) was measured in plasma before and after treatment. 35 patients were evaluated at 8 dose levels, including paclitaxel at 135 mg/m2 (158 μmol/m2) and Compound (1) at 44 mg/m2, and paclitaxel at 175 mg/m2 (205 μmol/m2) and Compound (1) at a doses ranging among 44-525 mg/m2 (110-1311 μmol /m2). Table 1 shows the eight different doses #1-#8 in mg/m^2 and μmol/m^2.

Table 1	#1	#2	#3	#4	#5	#6	#7	#8
Compound (1), mg/m^2	44	44	88	175	263	350	438	525
Compound (1), μmol/m^2	110	110	220	437	657	874	1094	1311
Paclitaxel, mg/m^2	135	175	175	175	175	175	175	175
Paclitaxel, μmol/m^2	158	205	205	205	205	205	205	205

No serious effects specifically attributable to Compound (1) were observed. Paclitaxel dose limiting toxicities occurred in a single patient in each of the top three dose levels (neutropenia, arthralgia, and febrile neutropenia with mucositis) resulting in cohort expansion. Compound (1) exhibited linear PK that was unaffected by paclitaxel dose, and was rapidly eliminated from plasma with terminal-phase half life of 0.94 ± 0.23 hours (h) and total body clearance of 28 ± 8 Liters/hour/meter^2 (L/h/m^2). Its apparent volume of distribution was comparable to total body water (V_{ss} 23 ± 16 L/m^2). Paclitaxel PK appeared to be moderately dependent on the Compound (1) dose, as indicated by a significant trend toward decreasing clearance, and increase in peak plasma concentration and V_{ss}, but without affecting the terminal phase half-life. These observations are consistent with competitive inhibition of paclitaxel hepatic metabolism. Increased toxicity at higher dose levels was consistent with a moderate increase in systemic exposure to paclitaxel. Induction of Hsp70 protein in plasma was dose dependent, peaking between about 8 hours to about 24 hours after dosing.

FIGs 1A, 1B, and 1C are bar graphs showing the percent increase in Hsp70 plasma levels associated with administration of the Compound (1)/paclitaxel combination therapy at 1 hour (FIG 1A), 5 hours (FIG 1B), and 8 hours (FIG 1C) after administration. Significant rises in Hsp70 levels occurred for at least one patient at the 88 mg/m2 (220 μmol /m2) Compound (1) dose, where Hsp70 levels nearly doubled in a percent increase of about 90%. At the 175 mg/m2 (437 μmol/m2) Compound (1) dose, Hsp70 concentrations more than doubled in two patients; at the 263 mg/m2 (657 μmol/m2) Compound (1) dose, Hsp70 concentrations roughly doubled in two patients and increased by more than 250% in a third patient; at the 350 mg/m2 (874 μmol/m2) Compound (1) dose, Hsp70 concentrations increased more than 200% in all patients and increased by as much as 500% in two patients; at the 438 mg/m2 (1094 μmol/m2) Compound (1) dose, Hsp70 concentrations roughly doubled in two patients, increased by over 2005 in one patient, and increased by as much as 500% in another patient.

Time to progression will be measured as the time from patient randomization to the time the patient is first recorded as having tumor progression according to the RECIST (Response Evaluation Criteria in Solid Tumors Group) criteria; see Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-16, the entire teachings of which are incorporated by reference. Death from any cause will be considered as progressed.

Time to progression can be performed on the randomized sample as well as the efficacy sample. Treatment groups can be compared using the log-rank test and Kaplan-Meier curves of time to progression can be presented.

Thus, the combination of a bi(thio-hydrazide) amide and taxane dramatically increased plasma Hsp70 levels in patients, giving significant increases for patients at a combined paclitaxel dose of 175 mg/m2 (205 μmol/m2) and Compound (1) doses ranging from 88 through 438 mg/m2 (220-1094 μmol/m2). Moreover, the combination was well-tolerated, with adverse events consistent with those expected for paclitaxel alone.

Example 4: A 2 Stage Phase 2 Study Shows the Disclosed Combination Therapy is Effective for Treating Advanced Metastatic Melanoma

The following study of Compound (1) and paclitaxel in patients with advanced metastatic melanoma was initiated based on the biological activity shown by the results of the above Phase I study, where the combined administration Compound (1) and paclitaxel led to dose-related Hsp70 induction.

The study included a Stage 1 initial safety assessment of the weekly dose schedule, where Compound (1) 106 mg/m2 (265 μmol/m2) and paclitaxel at 80 mg/m2 (94 μmol/m2) were administered weekly for 3 weeks out a 4 week period. The dose of Compound (1) was then escalated to 213 mg/m2 (532 μmol/m2) in combination with the paclitaxel at 80 mg/m2 (94 μmol/m2). The higher tolerated dose level was expanded to a total of 20 patients (Stage 1).

A total of 7 patients were treated in the initial safety assessment, 3 at the lower dose level and 4 at the higher. In the absence of dose-limiting toxicities in either group, the higher dose level was chosen as the dose of interest and additional patients were enrolled to complete stage 1. Adverse events seen were as expected for paclitaxel chemotherapy administration. Of 20 evaluable patients, 11 were stable at 3 months for 55% NPR.

The study will continue to Stage 2 if 7 or more patients have a response of stable disease or better, or at least 2 patients have a partial response or better. A safety assessment was performed with the first 6 patients enrolled a s the weekly dose schedule had not previously been studied in humans. The primary endpoint is non-progression rate (NPR) at 3 months and response rate. Pharmacodynamic parameters include pre and post-dose NK cell activity in blood and when possible, tumor biopsies.

Table 2 shows the significant preliminary results of anticancer efficacy and NK cell activity results when assayed 7 days after the second dose for different subjects. The Effector/Target data shows the ratio of the subjects PBMC cells to the NK assay target cells. The pre and post dose column values show the percent of tumor cells lysed before dosing with Paclitaxel and Compound (1). Best Response indicates an evaluation of the patient's tumor: SD indicates less than 20% of an increase and less

than 30% of a decrease in the sum of the longest diameters as compared to baseline; and PD = at least a 20% increase in the sum of the longest diameters as compared to baseline. NK Activity indicates the change in NK activity before and after dosing.

Table 2 shows that for patients completing the study (#12-#20, #22), three patients had less than 20% of an increase and less than 30% of a decrease in the sum of the longest diameters as compared to baseline, while seven patients had at least a 20% increase in the sum of the longest diameters as compared to baseline. For NK cell activity, four of the original patients showed a statistically significant increase between pre- and post-dose treatment.

Table 2		% tumor cell lysis		dosing information		Best Response	
Subject	Effector/ Target	pre-dose	post-dose	Paclitaxel, mg/M^2	Cmpnd (1) mg/M^2	cycle 2 week 4	NK activity
12	80:1	2.32	7.74	80	106	SD	increase
13	80:1	6.13	2.43	80	106	PD	decrease
14	80:1	3.83	10.77	80	213	SD	increase
15	(40:1)	3.5	10.01	80	213	PD	(increase)
16	80:1	19.71	19.78	80	213	SD	no change
17	80:1	41.61	26.52	80	213	PD	decrease
18	80:1	8.6	8.64	80	213	PD	no change
19	80:1	24.76	18.77	80	213	PD	decrease
20	80:1	16.49	5.2	80	213	PD	decrease
21	80:1	15.4	26.31	80	213	NA	increase
22	80:1	10.81	7.2	80	213	PD	decrease

The combination therapy was well-tolerated on the weekly schedule. Enrollment in the randomized portion will assess the activity of Compound (1) in combination with paclitaxel versus paclitaxel alone.

Stage 2 is planned to be a randomized 2-arm study comparing the drug combination to paclitaxel alone. The criterion for continuation to Stage 2 is >= 50% non-progression rate (NPR) at two months. A total of 78 patients are to be randomized 2:1 (combination:control). The primary endpoint is time to progression; secondary endpoints are response rate, survival, and quality of life. Pharmacodynamic parameters will include pre- and post-dose measurements of NK cell activity in blood and, when possible, tumor biopsies.

Example 5: A Phase 2 Study Shows the Disclosed Combination Therapy is Effective for Treating Soft Tissue Sarcomas

The following study of Compound (1) and paclitaxel in patients with soft tissue sarcomas was initiated based on the biological activity shown by the results of the above Phase I study, where the combined administration Compound (1) and paclitaxel led to dose-related Hsp70 induction.

The study is a 2 stage design, enrolling 30 patients in the first stage and adding 50 patients to total 80 if certain continuation criteria are met. Major inclusion criteria are refractory or recurrent soft tissue sarcomas other than gastrointestinal stromal tumor (GIST), with evidence of recent progression. Patients are treated weekly, 3 weeks out of every 4 week cycle with 213 mg/m2 Compound (1) and 80 mg/m2 paclitaxel. For example, the compounds were administered together 3 weeks out of 4 on Days 1, 8, and 15 of a 28 day cycle as a 1 hour IV infusion. 30 Patients have been enrolled to completed accrual of Stage 1.

As used herein, "soft-tissue sarcomas" (STS)are cancers that begin in the soft tissues that support, connect, and surround various parts of the body for example, soft tissues such as muscles, fat, tendons, nerves, and blood vessels, lymph nodes, or the like. Such STSs can occur anywhere in the body, though typically about one half occur in the limbs. In various embodiments, STSs can include one or more cancers selected from liposarcoma, fibrosarcoma, malignant fibrous histiocytoma leiomyosarcoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, or the like.

Table 3 shows the significant preliminary results of anticancer efficacy and NK cell activity results when assayed 7 days after the second dose for different subjects. The Effector/Target data shows the ratio of the subjects PBMC cells to the NK assay target cells. The pre and post dose column values show the percent of tumor cells lysed before dosing with Paclitaxel and Compound (1). Best Response indicates an evaluation of the patient's tumor: PR = at least a 30% decrease in the sum of the longest diameters as compared to baseline; SD indicates less than 20% of an increase and less than 30% of a decrease in the sum of the longest diameters as compared to baseline; and

PD = at least a 20% increase in the sum of the longest diameters as compared to baseline. NK Activity indicates the change in NK activity before and after dosing.

Table 3 shows that for patients completing the study (#23-#29, #31-33), five patients had less than 20% of an increase and less than 30% of a decrease in the sum of the longest diameters as compared to baseline, while five patients had at least a 20% increase in the sum of the longest diameters as compared to baseline. For NK cell activity, seven of the original patients showed a statistically significant increase or no change between pre- and post-dose treatment, while only four of the original patients showed a decrease statistically significant increase between pre- and post-dose treatment.

Table 3		% tumor cell lysis		dosing information		Best Response	
Subject	Effector/ Target	pre-dose	post-dose	Paclitaxel, mg/M^2	Cmpnd (1) mg/M^2	cycle 2	NK activity
23	80:1	4.28	30.48	80	213	PD	increase
24	80:1	20.74	20.04	80	213	SD	no change
25	80:1	34.28	11.86	80	213	PD	decrease
26	80:1	22.33	14.74	80	213	SD	decrease
27	80:1	10.6	22.9	80	213	SD	increase
28	80:1	17.93	28.13	80	213	SD	increase
29	80:1	6.58	17.18	80	213	PD	increase
30	(40:1)	9.88	9.91	80	213	NA	no change
31	80:1	2.62	5.46	80	213	SD	increase
32	80:1	13.03	7.41	80	213	PD	decrease
33	80:1	15.77	7.84	80	213	PD	decrease

Patients are currently being evaluated through 3 months. Adverse events seen were typical for paclitaxel administration on a similar schedule. Assessment of NK activity is ongoing. The addition of Compound (1) to the weekly paclitaxel schedule was well-tolerated. Stage 1 accrual has completed, and patients are currently being evaluated for the study continuation decision.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that

various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

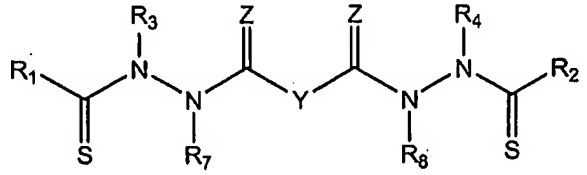
CLAIMS

What is claimed is:

1. A method of treating a subject with cancer, comprising the step of co-administering to the subject over three to five weeks:

a taxane in an amount of between about 243 μmol/m2 to 315 μmol/m2; and

a bis(thiohydrazide amide) in an amount between about 1473 μmol/m2 and about 1722 μmol/m2, wherein the bis(thiohydrazide amide) represented by the following Structural Formula:



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

2. The method of Claim 1, wherein the subject is human.

3. The method of Claim 2, wherein the cancer is metastatic melanoma or a soft tissue sarcoma other than a gastrointestinal stromal tumor.

4. The method of Claim 3, wherein the the taxane and the bis(thio-hydrazide) amide are each administered in three equal weekly doses for three weeks of a four week period.

5. The method of Claim 4, further comprising repeating the four week administration period until the cancer is in remission.

6. The method of Claim 4, wherein the taxane is paclitaxel intravenously administered in a weekly dose of about 94 μmol/m2.

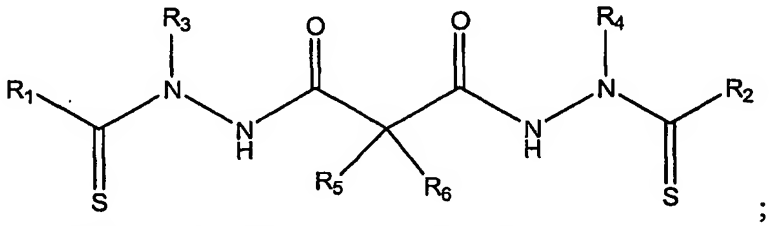
7. The method of Claim 4, wherein the bis(thiohydrazide amide) is intravenously administered in a weekly dose of between about 500 μmol/m2 and about 562 μmol/m2.

8. The method of Claim 5, wherein the bis(thiohydrazide amide) is intravenously administered in a weekly dose of about 532 μmol/m2.

9. The method of Claim 8, wherein the subject is treated for metastatic melanoma.

10. The method of Claim 8, wherein the subject is treated for a soft tissue sarcoma other than a gastrointestinal stromal tumor.

11. The method of Claim 1, wherein the bis(thiohydrazide amide) is represented by the following structural formula:



;

or the disodium or dipotassium salt thereof, wherein:

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 4-methoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 3-cyanophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 3-fluorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 4-chlorophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 3-methoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2,5-dichlorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethylphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is methyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is ethyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is *n*-propyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both methyl;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 is methyl, and R_4 is ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2-phenylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-phenylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclobutyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopentyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl; R_3 and R_4 are both phenyl; R_5 and R_6 are both -H;

R_1 and R_2 are both methyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both methyl; R_3 and R_4 are both *t*-butyl; R_5 and R_6 are both -H;

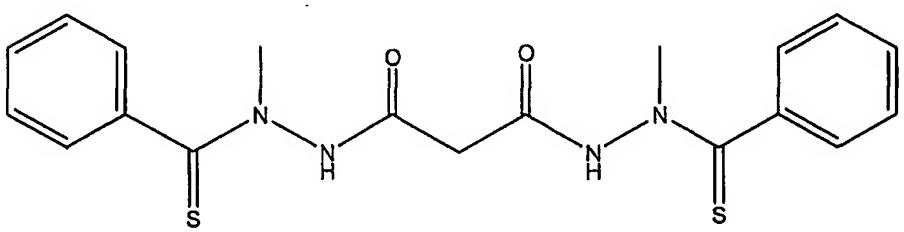
R_1 and R_2 are both methyl; R_3 and R_4 are both phenyl; R_5 and R_6 are both -H;

R_1 and R_2 are both *t*-butyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are ethyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H; or

R_1 and R_2 are both *n*-propyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H.

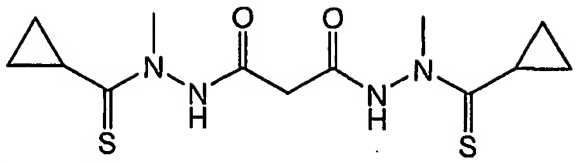
12. The method of Claim 1, wherein the bis(thiohydrazide amide) is:



;

or the disodium or dipotassium salt thereof.

13. The method of Claim 1, wherein the bis(thiohydrazide amide) is:

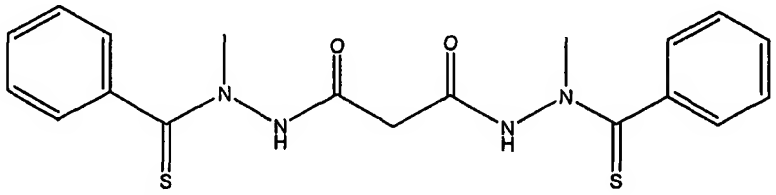


or the disodium or dipotassium salt thereof.

14. A method of treating a human subject with cancer, comprising intravenously administering to the subject in a four week period, three equal weekly doses of:

paclitaxel in an amount of about 94 μmol/m2; and

a bis(thiohydrazide amide) represented by the following Structural Formula:



or a pharmaceutically acceptable salt or solvate thereof in an amount of about 532 μmol/m2,

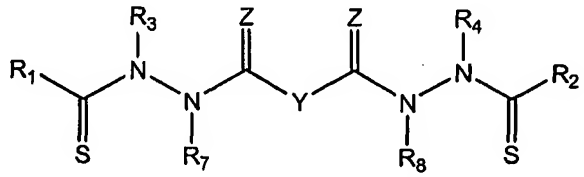
wherein the cancer is metastatic melanoma or a soft tissue sarcoma other than a gastrointestinal stromal tumor.

15. The method of Claim 14, wherein the subject is treated for metastatic melanoma.

16. A method of treating a subject with cancer, comprising administering to the subject once every three weeks, independently or together:

a) a taxane in an amount of about 205 μmol/m2; and

b) a bis(thiohydrazide amide) represented by the following Structural Formula:



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or a pharmaceutically acceptable salt or solvate thereof in an amount between about 220 μmol/m2 and about 1310 μmol/m2,

wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

17. The method of Claim 16, wherein the subject is human.

18. The method of Claim 17, wherein the cancer is metastatic melanoma or a soft tissue sarcoma other than a gastrointestinal stromal tumor.

19. The method of Claim 18, wherein the taxane is paclitaxel intravenously administered in an amount of about 205 μmol/m2.

20. The method of Claim 19, wherein the bis(thiohydrazide amide) is intravenously administered between about 220 μmol/m2 and about 1093 μmol/m2.

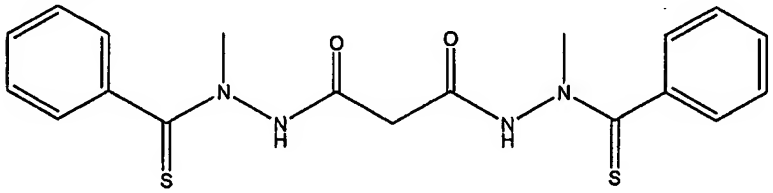
21. The method of Claim 20, wherein the bis(thiohydrazide amide) is in an amount of between about 749 μmol/m2 and about 999 μmol/m2.

22. The method of Claim 21, wherein the bis(thiohydrazide amide) is in an amount of between about 811 μmol/m2 and about 936 μmol/m2.

23. A method of treating a subject with cancer, comprising intraveneously administering to the subject in a single dose per three week period:

a) paclitaxel in an amount of about 205 μmol/m2; and

b) a bis(thiohydrazide amide) represented by the following Structural Formula:



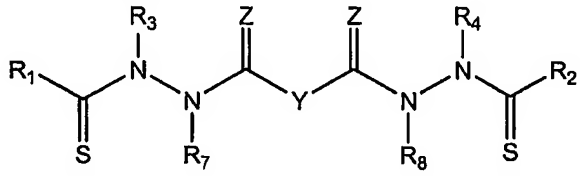
or a pharmaceutically acceptable salt or solvate thereof in an amount of about 874 μmol/m2,

wherein the cancer is metastatic melanoma or a soft tissue sarcoma other than a gastrointestinal stromal tumor.

24. A pharmaceutical composition, comprising:

a pharmaceutically acceptable carrier or diluent; and

a molar ratio of a bis(thiohydrazide amide) to a taxane between about 5.5:1 and about 5.9:1, wherein the bis(thiohydrazide amide) represented by the following Structural Formula:



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen

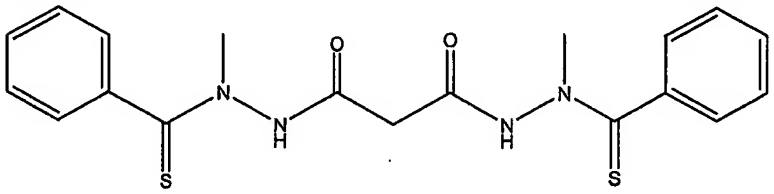
atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

25. The pharmaceutical composition of Claim 24, wherein the molar ratio of the bis(thiohydrazide amide) to the taxane is between about 5.6:1 and about 5.8:1, and the taxane is paclitaxel or a pharmaceutically acceptable salt or solvate thereof.

26. The pharmaceutical composition of Claim 25, wherein the bis(thiohydrazide amide) is a compound represented by the following Structural Formula:

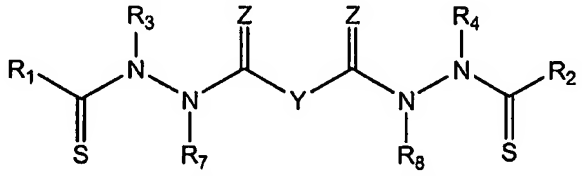


or a pharmaceutically acceptable salt or solvate thereof and is in a molar ratio to the paclitaxel of about 5.7:1.

27. A pharmaceutical composition, comprising:

a pharmaceutically acceptable carrier or diluent; and

a molar ratio of a bis(thiohydrazide amide) to a taxane between about 2.6:1 to about 3.0:1, wherein the bis(thiohydrazide amide) represented by the following Structural Formula:



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

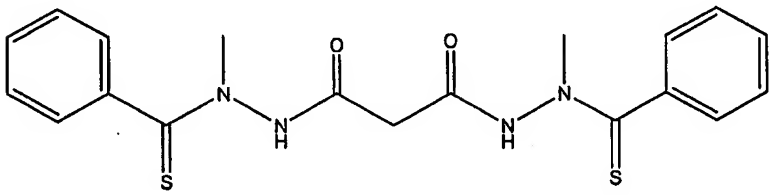
R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

28. The pharmaceutical composition of Claim 27, wherein the molar ratio of the bis(thiohydrazide amide) to the taxane is between about 2.7:1 and about 2.9:1, and the taxane is paclitaxel or a pharmaceutically acceptable salt or solvate thereof.

29. The pharmaceutical composition of Claim 28, wherein the bis(thiohydrazide amide) is a compound represented by the following Structural Formula:

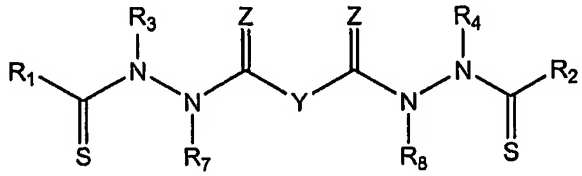


or a pharmaceutically acceptable salt or solvate thereof and is in a molar ratio to the paclitaxel of about 2.8:1.

30. A pharmaceutical composition, comprising:

a pharmaceutically acceptable carrier or diluent; and

a molar ratio of a bis(thiohydrazide amide) to a taxane between about 4.1:1 to about 4.5:1, wherein the bis(thiohydrazide amide) represented by the following Structural Formula:



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

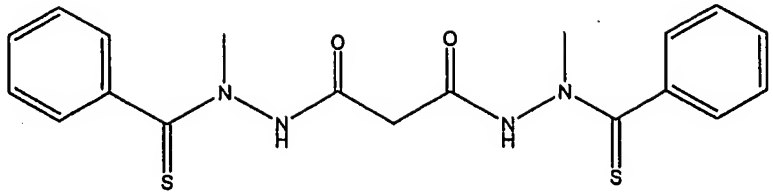
R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

31. The pharmaceutical composition of Claim 24, wherein the molar ratio of the bis(thiohydrazide amide) to the taxane is between about 4.2:1 and about 4.4:1, and the taxane is paclitaxel or a pharmaceutically acceptable salt or solvate thereof.

32. The pharmaceutical composition of Claim 25, wherein the bis(thiohydrazide amide) is a compound represented by the following Structural Formula:



or a pharmaceutically acceptable salt or solvate thereof and is in a molar ratio to the paclitaxel of about 4.3:1.

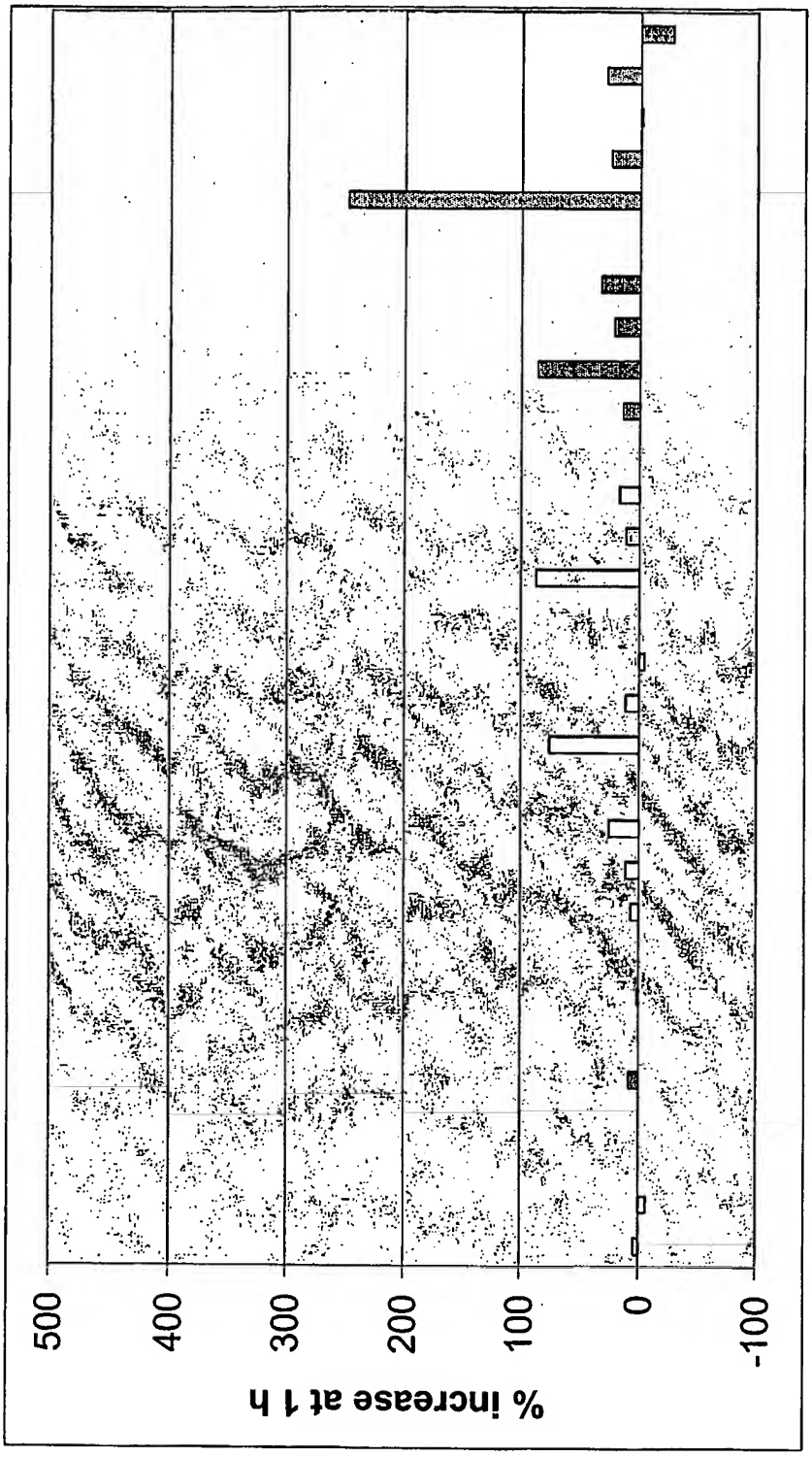


FIG 1A

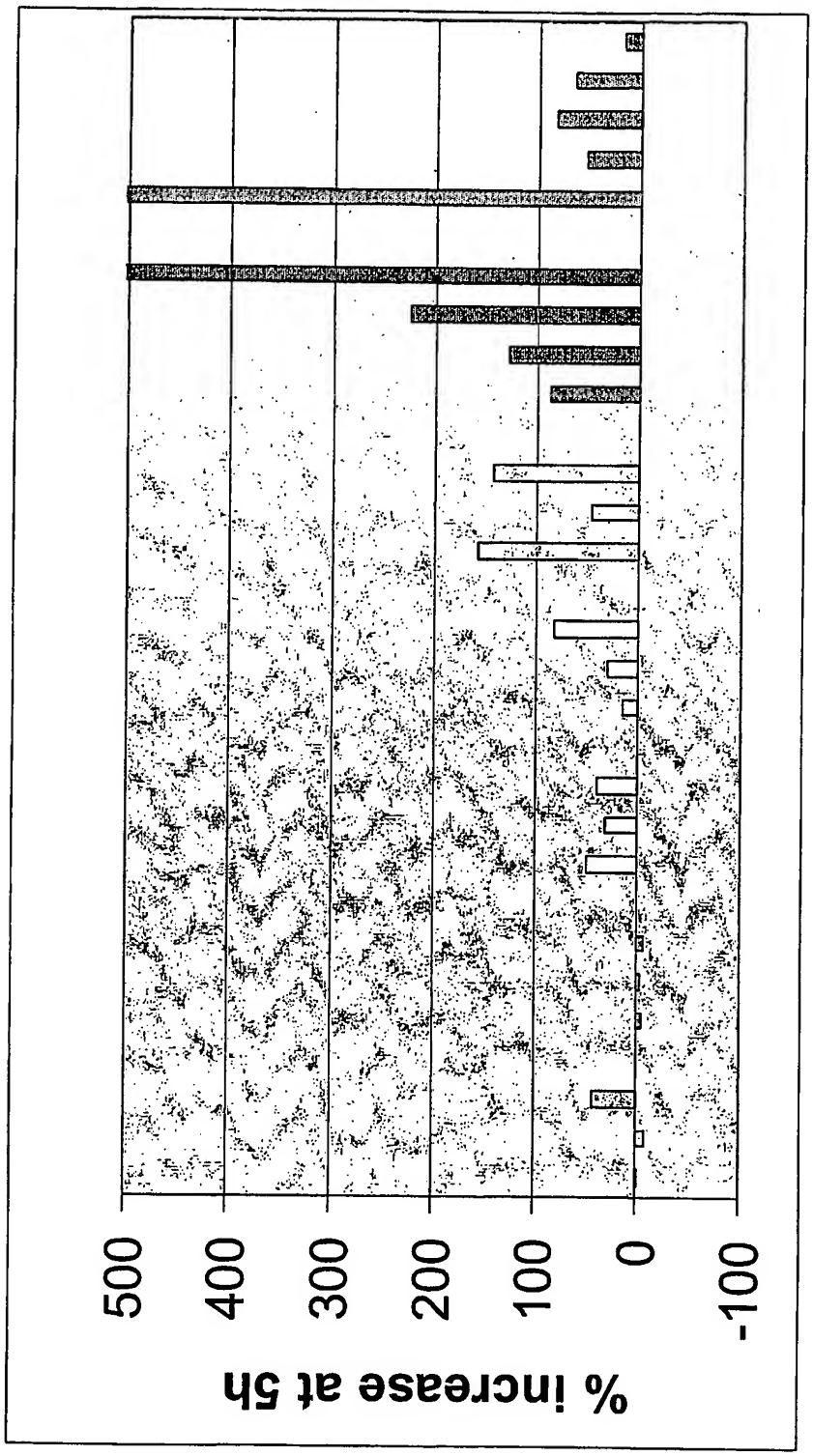


FIG 1B

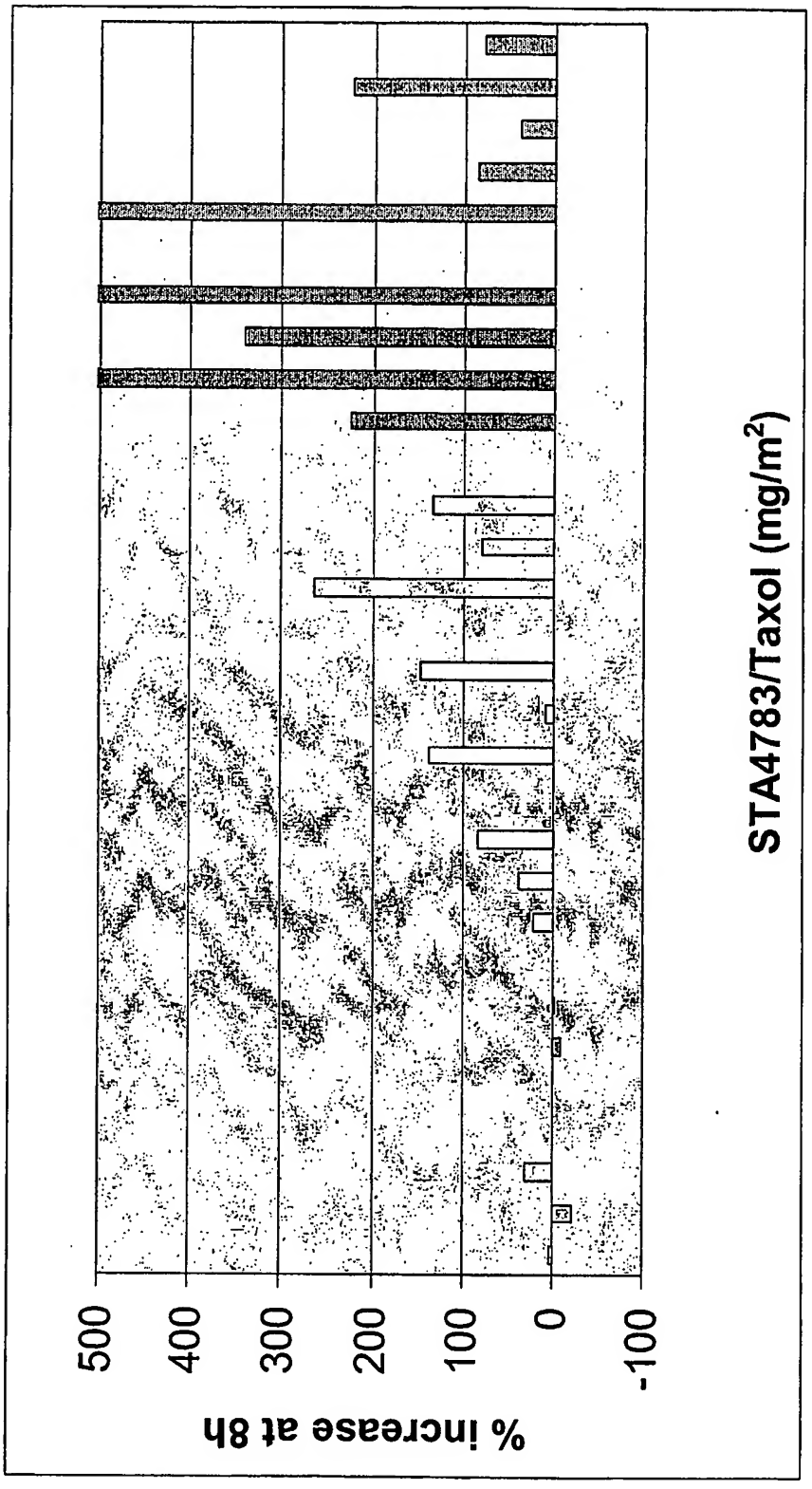


FIG 1C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/014531

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/337 A61K31/165 A61K31/16 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 03/006428 A (SBR PHARMACEUTICALS CORP; KOYA, KEIZO; SUN, LIJUN; CHEN, SHOUJUN; TATS) 23 January 2003 (2003-01-23) page 29	1-32
X,Y	US 2003/195258 A1 (KOYA KEIZO ET AL) 16 October 2003 (2003-10-16) example 16	1-32

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2006	07/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/014531

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03006428 A	23-01-2003	BR 0211228 A	10-08-2004
		CA 2454120 A1	23-01-2003
		CN 1553894 A	08-12-2004
		EP 1406870 A1	14-04-2004
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		MX PA04000243 A	07-03-2005
		NZ 530964 A	26-08-2005
US 2003195258 A1	16-10-2003	NONE	